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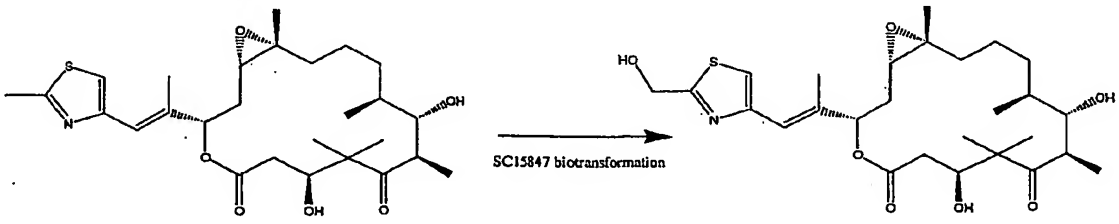
(54) Title: COMPOSITIONS AND METHODS FOR HYDROXILATING EPOTHILONES



epothilone B epothilone F

(57) Abstract: Isolated nucleic acid sequences and polypeptides encoded thereby for epothilone B hydroxylase and mutants and variants thereof and a ferredoxin located downstream from the epothilone B hydroxylase gene are provided. Also provided are vectors and cells containing these vectors. In addition, methods for producing recombinant microorganisms, methods for using these recombinant microorganism to produce hydroxyalkyl-bearing epothilones and an epothilone analog produced by a mutant of epothilone B hydroxylase are provided.

WO 2004/061116 A2

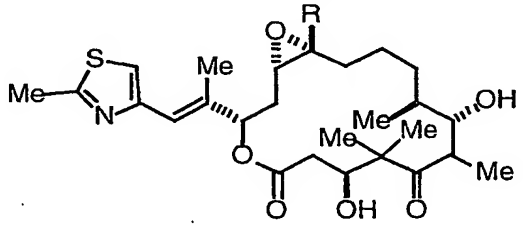
COMPOSITIONS AND METHODS FOR HYDROXYLATING EPOTHILONES

Field of the Invention

The present invention relates to isolated nucleic acids sequences and polypeptides encoded thereby for epothilone B hydroxylase and mutants and variants thereof, and a ferredoxin located downstream from the epothilone B hydroxylase gene. The present invention also relates to recombinant microorganisms expressing epothilone B hydroxylase or a mutant or variant thereof and/or ferredoxin which are capable of hydroxylating small organic molecule compounds, such as epothilones, having a terminal alkyl group to produce compounds having a terminal hydroxyalkyl group. Also provided are methods for recombinantly producing such microorganisms as well as methods for using these recombinant microorganisms in the synthesis of compounds having a terminal hydroxylalkyl group. The compositions and methods of the present invention are useful in preparation of epothilones having a variety of utilities in the pharmaceutical field. A novel epothilone analog produced using a mutant of epothilone B hydroxylase of the present invention is also described.

Background of the Invention

Epothilones are macrolide compounds that find utility in the pharmaceutical field. For example, epothilones A and B having the structures:



Epothilone A R=H

Epothilone B R=Me

have been found to exert microtubule-stabilizing effects similar to paclitaxel (TAXOL®) and hence cytotoxic activity against rapidly proliferating cells, such as,

tumor cells or cells associated with other hyperproliferative cellular diseases, see Bollag *et al.*, Cancer Res., Vol. 55, No. 11, 2325-2333 (1995).

Epothilones A and B are natural anticancer agents produced by *Sorangium cellulosum* that were first isolated and characterized by Hofle *et al.*, DE 4138042; WO 93/10121; Angew. Chem. Int. Ed. Engl. Vol. 35, No13/14, 1567-1569 (1996); and J. Antibiot., Vol. 49, No. 6, 560-563 (1996). Subsequently, the total syntheses of epothilones A and B have been published by Balog *et al.*, Angew. Chem. Int. Ed. Engl., Vol. 35, No. 23/24, 2801-2803, 1996; Meng *et al.*, J. Am. Chem. Soc., Vol. 119, No. 42, 10073-10092 (1997); Nicolaou *et al.*, J. Am. Chem. Soc., Vol. 119, No. 34, 7974-7991 (1997); Schinzer *et al.*, Angew. Chem. Int. Ed. Eng., Vol. 36, No. 5, 523-524 (1997); and Yang *et al.*, Angew. Chem. Int. Ed. Engl., Vol. 36, No. 1 / 2, 166-168, 1997. WO 98/25929 disclosed the methods for chemical synthesis of epothilone A, epothilone B, analogs of epothilone and libraries of epothilone analogs. The structure and production from *Sorangium cellulosum* DSM 6773 of epothilones C, D, E, and F was disclosed in WO 98/22461. Figure 1 provides a diagram of the biotransformation as described in WO 00/39276 of epothilone B to epothilone F in *Actinomycetes species* strain SC15847 (ATCC PT-1043), subsequently identified as *Amycolatopsis orientalis*.

Cytochrome P450 enzymes are found in prokaryotes and eukaryotic cells and have in common a heme binding domain which can be distinguished by an absorbance peak at 450 nm when complexed with carbon monoxide. Cytochrome P450 enzymes perform a broad spectrum of oxidative reactions on primarily hydrophobic substrates including aromatic and benzylic rings, and alkanes. In prokaryotes they are found as detoxifying systems and as a first enzymatic step in metabolizing substrates such as toluene, benzene and camphor. Cytochrome P450 genes have also been found in biosynthetic pathways of secondary metabolites such as nikkomycin in *Streptomyces tendae* (Bruntner, C. et al, 1999, Mol. Gen. Genet. 262: 102-114), doxorubicin (Dickens, M.L, Strohl, W.R., 1996, J. Bacteriol, 178: 3389-3395) and in the epothilone biosynthetic cluster of *Sorangium cellulosum* (Julien, B. et al., 2000, Gene, 249: 153-160). With a few exceptions, the cytochrome P450 systems in prokaryotes are composed of three proteins; a ferredoxin NADH or NADPH dependent reductase, an iron-sulfur ferredoxin and the cytochrome P450

enzyme (Lewis, D.F., Hlavica, P., 2000, Biochim. Biophys. Acta., 1460: 353-374). Electrons are transferred from ferredoxin reductase to the ferredoxin and finally to the cytochrome P450 enzyme for the splitting of molecular oxygen.

Summary of the Invention

An object of the present invention is to provide isolated nucleic acid sequences encoding epothilone B hydroxylase and variants or mutants thereof and isolated nucleic acid sequences encoding ferredoxin or variants or mutants thereof.

Another object of the present invention is to provide isolated polypeptides comprising amino acid sequences of epothilone B hydroxylase and variants or mutants thereof and isolated polypeptides comprising amino acid sequences of ferredoxin and variants or mutants thereof.

Another object of the present invention is to provide structure coordinates of the homology model of the epothilone B hydroxylase. The structure coordinates are listed in Appendix 1. This model of the present invention provides a means for designing modulators of a biological function of epothilone B hydroxylase as well as additional mutants of epothilone B hydroxylase with altered specificities.

Another object of the present invention is to provide vectors comprising nucleic acid sequences encoding epothilone B hydroxylase or a variant or mutant thereof and/or ferredoxin or a variant or mutant thereof. In a preferred embodiment, these vectors further comprise a nucleic acid sequence encoding ferredoxin.

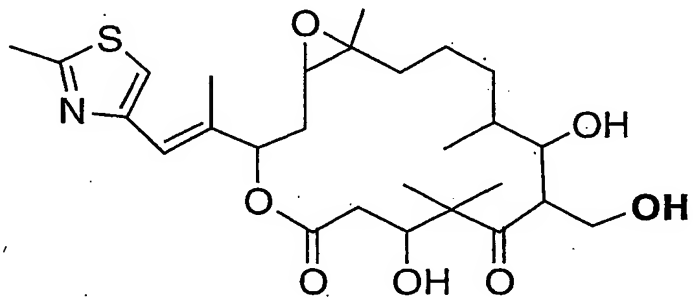
Another object of the present invention is to provide host cells comprising a vector containing a nucleic acid sequence encoding epothilone B hydroxylase or a variant or mutant thereof and/or ferredoxin or a variant or mutant thereof.

Another object of the present invention is to provide a method for producing recombinant microorganisms that are capable of hydroxylating compounds, and in particular epothilones, having a terminal alkyl group to produce compounds having a terminal hydroxyalkyl group.

Another object of the present invention is to provide microorganisms produced recombinantly which are capable of hydroxylating compounds, and in particular epothilones, having a terminal alkyl group to produce compounds having a terminal hydroxyalkyl group.

Another object of the present invention is to provide methods for hydroxylating compounds in these recombinant microorganisms. In particular, the present invention provides a method for the preparation of hydroxyalkyl-bearing epothilones, which compounds find utility as antitumor agents and as starting materials in the preparation of other epothilone analogs.

Yet another object of the present invention is to provide a compound of Formula A:



referred to herein as 24-OH epothilone B or 24-OH EpoB, as well as compositions and methods for production of compositions comprising the compound of Formula A.

Brief Description of the Figures

Figure 1 provides a schematic of the biotransformation as set forth in WO 00/39276, U.S. Application Serial No. 09/468,854, filed December 21, 1999, of epothilone B to epothilone F by *Amycolatopsis orientalis* strain SC15847 (PTA1043).

Figure 2 shows the nucleic acid sequence alignments of SEQ ID NO:5 through SEQ ID NO:22 used to design the PCR primers for cloning of the nucleic acid sequence encoding epothilone B hydroxylase.

Figure 3 shows the sequence alignment between epothilone B hydroxylase (SEQ ID NO:2) and EryF (PDB code 1JIN chain A; SEQ ID NO:76). The asterisks indicate sequence identities, the colons (:) similar residues.

Figure 4 provides a homology model of epothilone B hydroxylase based upon sequence alignment with EryF as shown in Figure 3.

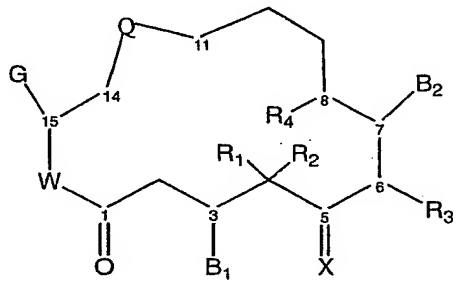
Figure 5 shows an energy plot of the epothilone B hydroxylase model (indicated by dashed line) relative to EryF (PDB code 1JIN; indicated by solid line). An averaging window size of 51 residues was used, i.e., the energy at a given residue

position is calculated as the average of the energies of the 51 residues in the sequence that lie with the given residue at the central positions.

Detailed Description of the Invention

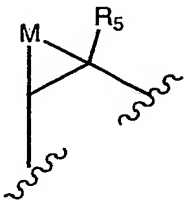
The present invention relates to isolated nucleic acid sequences and polypeptides and methods for obtaining compounds with desired substituents at a terminal carbon position. In particular, the present invention provides compositions and methods for the preparation of hydroxyalkyl-bearing epothilones, which compounds find utility as antitumor agents and as starting materials in the preparation of other epothilone analogs.

The term "epothilone," as used herein, denotes compounds containing an epothilone core and a side chain group as defined herein. The term "epothilone core," as used herein, denotes a moiety containing the core structure (with the numbering of ring system positions used herein shown):

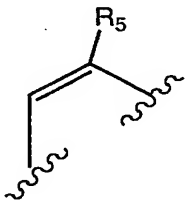


wherein the substituents are as follows:

Q is selected from the group consisting of



and



;

W is O or NR_6;

X is selected from the group consisting of O, H and OR_7;

M is O, S, NR_8, CR_9R_{10};

B_1 and B_2 are selected from the group consisting of OR_{11}, $OCOR_{12}$;

R_1-R_5 and R_{12}-R_{17} are selected from the group consisting of H, alkyl, substituted alkyl, aryl, and heterocyclo, and wherein R_1 and R_2 are alkyl they can be joined to form a cycloalkyl;

R_6 is selected from the group consisting of H, alkyl, and substituted alkyl;

R_7 and R_{11} are selected from the group consisting of H, alkyl, substituted alkyl, trialkylsilyl, alkyldiarylsilyl and dialkylarylsilyl;

R_8 is selected from the group consisting of H, alkyl, substituted alkyl, $R_{13}C=O$, $R_{14}OC=O$ and $R_{15}SO_2$; and

R_9 and R_{10} are selected from the group consisting of H, halogen, alkyl, substituted alkyl, aryl, heterocyclo, hydroxy, $R_{16}C=O$, and $R_{17}OC=O$.

The term "side chain group" refers to substituent G as defined above for Epothilone A or B or G_1 and G_2 as shown below.

G_1 is the following formula V

$$HO\text{-}CH_2\text{-}(A_1)_n\text{-}(Q)_m\text{-}(A_2)_o \qquad (V),$$

and

G_2 is the following formula VI

$$CH_3\text{-}(A_1)_n\text{-}(Q)_m\text{-}(A_2)_o \qquad (VI),$$

where

A_1 and A_2 are independently selected from the group of optionally substituted C_1-C_3 alkyl and alkenyl;

Q is optionally substituted ring system containing one to three rings and at least one carbon to carbon double bond in at least one ring; and

n, m, and o are integers independently selected from the group consisting of zero and 1, where at least one of m, n or o is 1.

The term "terminal carbon" or "terminal alkyl group" refers to the terminal carbon or terminal methyl group of the moiety either directly bonded to the epothilone core at position 15 or to the terminal carbon or terminal alkyl group of the side chain group bonded at position 15. It is understood that the term "alkyl group" includes alkyl and substituted alkyl as defined herein.

The term "alkyl" refers to optionally substituted, straight or branched chain saturated hydrocarbon groups of 1 to 20 carbon atoms, preferably 1 to 7 carbon atoms.

The expression "lower alkyl" refers to optionally substituted alkyl groups of 1 to 4 carbon atoms.

The term "substituted alkyl" refers to an alkyl group substituted by, for example, one to four substituents, such as, halo, trifluoromethyl, trifluoromethoxy, hydroxy, alkoxy, cycloalkyloxy, heterocyclooxy, oxo, alkanoyl, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, aralkylamino, cycloalkylamino, heterocycloamino, disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or aralkyl, alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino, thiol, alkylthio, arylthio, aralkylthio, cycloalkylthio, heterocyclothio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamido (e.g. SO_2NH_2), substituted sulfonamido, nitro, cyano, carboxy, carbamyl (e.g. $CONH_2$), substituted carbamyl (e.g. CONH alkyl, CONH aryl, CONH aralkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl), alkoxycarbonyl, aryl, substituted aryl, guanidino and heterocyclos, such as, indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like. Where noted above where the substituent is further substituted it will be with halogen, alkyl, alkoxy, aryl or aralkyl.

In accordance with one aspect of the present invention there are provided isolated polynucleotides that encode epothilone B hydroxylase, an enzyme capable of hydroxylating epothilones having a terminal alkyl group to produce epothilones having a terminal hydroxyalkyl group.

In accordance with another aspect of the present invention there are provided isolated polynucleotides that encode a ferredoxin, the gene for which is located downstream from the epothilone B hydroxylase gene. Ferredoxin is a protein of the cytochrome P450 system.

By "polynucleotides", as used herein, it is meant to include any form of DNA or RNA such as cDNA or genomic DNA or mRNA, respectively, encoding these enzymes or an active fragment thereof which are obtained by cloning or produced synthetically by well known chemical techniques. DNA may be double- or single-stranded. Single-stranded DNA may comprise the coding or sense strand or the non-coding or antisense strand. Thus, the term polynucleotide also includes

polynucleotides exhibiting at least 60% or more, preferably at least 80%, homology to sequences disclosed herein, and which hybridize under stringent conditions to the above-described polynucleotides. As used herein, the term "stringent conditions" means hybridization conditions of 60°C at 2xSSC buffer. More preferred are isolated nucleic acid molecules capable of hybridizing to the nucleic acid sequence set forth in 1, 30, 32, 34, 36, 37, 38, 39, 40, 41, 42, 60, 62, 64, 66, 68, 70, 72, or 74 or SEQ ID NO:3, or to the complementary sequence of the nucleic acid sequence set forth in SEQ ID NO:1, 30, 32, 34, 36, 37, 38, 39, 40, 41, 42, 60, 62 ,64, 66, 68, 70, 72 ,or 74 or SEQ ID NO:3, under hybridization conditions of 3X SSC at 65°C for 16 hours, and which are capable of remaining hybridized to the nucleic acid sequence set forth in SEQ ID NO:1, 30, 32, 34, 36, 37, 38, 39, 40, 41, 42, 60, 62, 64, 66, 68, 70, 72 or 74 or SEQ ID NO:3, or to the complementary sequence of the nucleic acid sequence set forth in SEQ ID NO:1, 30, 32, 34, 36, 37, 38, 39, 40, 41 or 42, 60, 62, 64, 66, 68, 70, 72 or 74 or SEQ ID NO:3, under wash conditions of 0.5X SSC, 55°C for 30 minutes.

In one embodiment, a polynucleotide of the present invention comprises the genomic DNA depicted in SEQ ID NO:1 or a homologous sequence or fragment thereof which encodes a polypeptide having similar activity to that of this epothilone B hydroxylase. Alternatively, a polynucleotide of the present invention may comprise the genomic DNA depicted in SEQ ID NO:3 or a homologous sequence or fragment thereof which encodes a polypeptide having similar activity to this ferredoxin. Due to the degeneracy of the genetic code, polynucleotides of the present invention may also comprise other nucleic acid sequences encoding this enzyme and derivatives, variants or active fragments thereof.

The present invention also relates to variants of these polynucleotides which may be naturally occurring, i.e., present in microorganisms such as *Amycolatopsis orientalis* and *Amycolata autotrophica,* or in soil or other sources from which nucleic acids can be isolated, or mutants prepared by well known mutagenesis techniques. Exemplary variants polynucleotides of the present invention are depicted in SEQ ID NO: 36-42.

By "mutants" as used herein it is meant to be inclusive of nucleic acid sequences with one or more point mutations, or deletions or additions of nucleic acids as compared to SEQ ID NO: 1 or 3, but which still encode a polypeptide or fragment

with similar activity to the polypeptides encoded by SEQ ID NO: 1 or 3. In a preferred embodiment, mutations are made which alter the substrate specificity and/or yield of the enzyme. A preferred region of mutation with respect to the epothilone B hydroxylase gene is that region of the nucleic acid sequence coding for the approximately 113 amino acids residues comprising the active site of the enzyme. Also preferred are mutants encoding a polypeptide with at least one amino acid substitution at amino acid position GLU31, ARG67, ARG88, ILE92, ALA93, VAL106, ILE130, ALA140, MET176, PHE190, GLU 231, SER294, PHE237, or ILE365 of SEQ ID NO:1. Exemplary polynucleotide mutants of the present invention are depicted in SEQ ID NO: 30, 32, 34, 60, 62, 64, 66, 68, 70, 72 and 74.

Cloning of the nucleic acid sequence of SEQ ID NO:1 encoding epothilone B hydroxylase was performed using PCR primers designed by aligning the nucleic acid sequences of six cytochrome P450 genes from bacteria. The following cytochrome P450 genes were aligned:

Sequence 1: Locus: STMSUACB; Accession number: M32238; Reference: Omer, C.A., J. Bacteriol. 172: 3335-3345 (1990)

Sequence 2: Locus: STMSUBCB; Accession number: M32239; Reference: Omer, C.A., J. Bacteriol. 172: 3335-3345 (1990)

Sequence 3: Locus: AB018074 (formerly STMORFA); Accession number: AB018074; Reference: Ueda, K., J. Antibiot. 48: 638-646 (1995)

Sequence 4: Locus: SSU65940; Accession number: U65940; Reference: Motamedi, H., J. Bacteriol. 178: 5243-5248 (1996)

Sequence 5: Locus: STMOLEP; Accession number: L37200; Reference: Rodriguez, A.M., FEMS Microbiol. Lett. 127: 117-120 (1995)

Sequence 6: Locus: SERCP450A; Accession number: M83110; Reference: Andersen, J.F. and Hutchinson, C.R., J. Bacteriol. 174: 725-735 (1992)

Alignments were performed using an implementation of the algorithm of Myers, E.W. and W. Miller. 1988. *CABIOS* 4:1, 11-17., the Align program from Scientific and Educational Software (Durham, North Carolina, USA). Three highly conserved regions were identified in the I-helix, containing the oxygen binding domain, in the K-helix, and spanning the B-bulge and L-helix containing the

conserved heme binding domain. Primers were designed to the three conserved regions identified in the alignment. Primers P450-1$^+$ (SEQ ID NO:23) and P450-1a$^+$ (SEQ ID NO:24) were designed from the I helix, Primer P450-2$^+$ (SEQ ID NO:25) was designed from the B-Bulge and L-helix region and Primer P450-3$^-$(SEQ ID NO:27) was designed as the reverse complement to the heme binding protein.

Genomic fragments were then amplified via polymerase chain reaction (PCR). After PCR amplification, the reaction products were separated by gel electrophoresis and fragments of the expected size were excised. The DNA was extracted from the agarose gel slices using the Qiaquick gel extraction procedure (Qiagen, Santa Clarita, California, USA). The fragments were then cloned into the PCRscript vector (Stratagene, La Jolla, California, USA) using the PCRscript Amp cloning kit (Stratagene). Colonies containing inserts were picked to 1-2 ml of LB broth with 100 µg/ml ampicillin, 30-37°C, 16-24 hours, 230-300 rpm. Plasmid isolation was performed using the Mo Bio miniplasmid prep kit (Mo Bio, Solano Beach, California, USA). This plasmid DNA was used as a PCR and sequencing template and for restriction digest analysis.

The cloned PCR products were sequenced using the Big-Dye sequencing kit from Applied Biosystems, (Foster City, California, USA) and were analyzed using the ABI310 sequencer (Applied Biosystems, Foster City, California, USA). The sequence of the inserts was used to perform a TblastX search, using the protocol of Altschul, S.F, *et al.*, Mol. Biol. 215:403-410 (1990), of the non-redundant protein database. Unique sequences having a significant similarity to known cytochrome P450 proteins were retained. Using this approach, a total of nine different P450 sequences were identified from SC15847, seven from the genomic DNA template and two from the cDNA. Two P450 sequences were found in common between the DNA and cDNA templates. Of the fifty cDNA clones analyzed, two sequences were predominant, with twenty clones each. These two genes were then cloned from the genomic DNA.

The nucleic acid sequence of the genomic DNA was determined using the Big-Dye sequencing system (Applied Biosystems) and analyzed using an ABI310 sequencer. This sequence is depicted in SEQ ID NO:1. An open reading frame coding for a protein of 404 amino acids and a predicted molecular weight of 44.7 kDa was found within the cloned BglII fragment. The deduced amino acid sequence of

this polypeptide is depicted in SEQ ID NO: 2. The amino acid sequence of this polypeptide was found to share 51% identity with the NikF protein of *Streptomyces tendae* (Bruntner, C. et al, 1999, Mol. Gen. Genet. 262: 102-114) and 48% identity with the Sca-2 protein of *S. carbophilus* (Watanabe, I. Et al, 1995, Gene 163: 81-85). Both of these enzymes belong to the cytochrome P450 family 105. The invariable cysteine found in the heme-binding domain of all cytochrome P450 enzymes is found at residue 356. This gene for epothilone B hydroxylase has been named *ebh*. The ATG start codon of a putative ferredoxin gene of 64 amino acids is found nine basepairs downstream from the stop codon of *ebh*. This enzyme was found to share 50% identity with ferredoxin genes of *S. griseoulus* (O'Keefe, D.P., et al, 1991, Biochemistry 30: 447-455) and *S. noursei* (Brautaset, T., et al, 2000, Chem. Biol. 7: 395-403). The nucleic acid sequence encoding this ferredoxin is depicted in SEQ ID NO:3 and the amino acid sequence for this ferredoxin polypeptide is depicted in SEQ ID NO:4.

The *ebh* gene sequence was also used to isolate variant cytochrome P450 genes from other microorganisms. Exemplary variant polynucleotides *ebh*43491, *ebh*14930, *ebh*53630, *ebh*53550, *ebh*39444, *ebh*43333 and *ebh*35165 of the present invention and the species from which they were isolated are depicted in Table 1 below. The nucleic acid sequences for these variants are depicted in SEQ ID NO:36-42, respectively.

Table 1: Variant polynucleotides

ATCC ID	Species	*ebh* gene designation
43491	*Amycolatopsis orientalis*	*ebh*43491
14930	*Amycolatopsis orientalis*	*ebh*14930
53630	*Amycolatopsis orientalis*	*ebh*53630
53550	*Amycolatopsis orientalis*	*ebh*53550
39444	*Amycolatopsis orientalis*	*ebh*39444
43333	*Amycolatopsis orientalis*	*ebh*43333
35165	*Amycolatopsis orientalis*	*ebh*35165

The amino acid sequences encoded by the exemplary variants *ebh*43491, *ebh*14930, *ebh*53630, *ebh*53550, *ebh*39444, *ebh*43333 and *ebh*35165 are depicted in

SEQ ID NO:43-49, respectively. Table 2 provides a summary of the amino acid substitutions of these exemplary variants.

Table 2: Amino acid Substitutions

Position	*ebh*	Substitution	*ebh* variant
100	Gly	Ser	*ebh*14930, *ebh*43333, *ebh*53550, *ebh*43491
101	Lys	Arg	*ebh*14930
130	Ile	Leu	*ebh*14930
192	Ser	Gln	*ebh*14930
224	Ser	Thr	*ebh*14930, *ebh*43333, *ebh*53550, *ebh*43491
285	Ile	Val	*ebh*14930, *ebh*43333, *ebh*53550, *ebh*43491
69	Ser	Asn	*ebh*43333
256	Val	Ala	*ebh*43333, *ebh*53550, *ebh*43491
93	Ala	Ser	*ebh*53550
326	Asp	Glu	*ebh*53550, *ebh*43491
333	Thr	Ala	*ebh*53550, *ebh*43491
133	Leu	Met	*ebh*43491
398	His	Arg	*ebh*39444

Mutations were also introduced into the coding region of the *ebh* gene to identify mutants with improved yield, and/or rate of bioconversion and/or altered substrate specificity. Exemplary mutant nucleic acid sequences of the present invention are depicted in SEQ ID NO:30, 32, 34, 60, 62, 64, 66, 68, 70, 72 and 74.

The nucleic acid sequence of SEQ ID NO:30 encodes a mutant *ebh*25-1 which exhibits altered substrate specificity. Plasmid pANT849*ebh*25-1 containing this mutant gene was deposited and accepted by an International Depository Authority under the provisions of the Budapest Treaty. The deposit was made on November 21, 2002 to the American Type Culture Collection at 10801 University Boulevard in Manassas, Virginia 20110-2209. The ATCC Accession Number is PTA-4809. All restrictions upon public access to this plasmid will be irrevocably removed upon granting of this patent application. The Deposit will be maintained in a public depository for a period of thirty years after the date of deposit or five years after the last request for a sample or for the enforceable life of the patent, whichever is longer. The above-referenced plasmid was viable at the time of the deposit. The deposit will be replaced if viable samples cannot be dispensed by the depository.

This *S. lividans* transformant identified in the screening of mutation 25 (primers NPB29-mut25f (SEQ ID NO:58) and NPB29-mut25r (SEQ ID NO:59)) was found to produce a product with a different HPLC elution time than epothilone B or

epothilone F. A sample of this unknown was analyzed by LC-MS and was found to have a molecular weight of 523 (M.W.), consistent with a single hydroxylation of epothilone B. Plasmid DNA was isolated from the *S. lividans* culture and used as a template for PCR amplification using primers NPB29-6f (SEQ ID NO:28) and NPB29-7r (SEQ ID NO:29) (see Example 17). The expected fragment was obtained and sequenced using the Big-Dye sequencing system. The *ebh*25-1 mutant was found to have two mutations resulting in changes in the amino acid sequence of the protein, asparagine 195 is changed to serine and serine 294 is changed to proline. The position targeted for mutation at codon 238 was found to have a two nucleotide change, which did not result in a change of the amino acid sequence of the protein. The amino acid sequence of the mutant polypeptide encoded by SEQ ID NO:30 is depicted in SEQ ID NO:31.

The nucleic acid sequence of SEQ ID NO:32 encodes a mutant *ebh*10-53, which exhibits improved bioconversion yield. This *S. lividans* transformant identified in the screening of mutation 10 (primers NPB29-mut10f (SEQ ID NO:54) and NPB29-mut10r (SEQ ID NO:55)) produced a greater yield of epothilone F. Plasmid DNA was isolated from the *S. lividans* culture and used as a template for PCR amplification using primers NPB29-6f (SEQ ID NO:28) and NPB29-7r (SEQ ID NO:29)(see Example 16). The expected fragment was obtained and sequenced using the Big-Dye sequencing system. The *ebh*10-53 mutant was found to have two mutations resulting in changes in the amino acid sequence of the protein, glutamic acid 231 is changed to arginine and phenylalanine 190 is changed to tyrosine. The position 231 was the target of the mutagenesis, the change at residue 190 is an inadvertent change that is an artifact of the mutagenesis procedure. The amino acid sequence of the mutant polypeptide encoded by SEQ ID NO:32 is depicted in SEQ ID NO:33.

The nucleic acid sequence of SEQ ID NO:34 encodes a mutant *ebh*24-16, which also exhibits improved bioconversion yield. This *S. lividans* transformant, *ebh*24-16 identified in the screening of mutation 24 (primers NPB29-mut24f (SEQ ID NO:56) and NPB29-mut24r (SEQ ID NO:57) also produced a greater yield of epothilone F. Plasmid DNA was isolated from the *S. lividans* culture and used as a template for PCR amplification using primers NPB29-6f (SEQ ID NO:28) and

NPB29-7r (SEQ ID NO:29). The expected fragment was obtained and sequenced using the Big-Dye sequencing system. The *ebh*24-16 mutant was found to have two mutations resulting in changes in the amino acid sequence of the protein, phenylalanine 237 is changed to alanine and isoleucine 92 is changed to valine. The position 237 was the target of the mutagenesis, the change at residue 92 is an inadvertent change that is an artifact of the mutagenesis procedure. The amino acid sequence of the mutant polypeptide encoded by SEQ ID NO:34 is depicted in SEQ ID NO:35.

The nucleic acid sequence of SEQ ID NO:60 encodes a mutant *ebh*24-16d8, which also exhibits improved bioconversion yield. This *S. rimosus* transformant, *ebh*24-16d8 identified in the screening of mutation 59 (primer NPB29mut59 (SEQ ID NO:70)) also produced a greater yield of epothilone F. Plasmid DNA was isolated from the *S. rimosus* culture and used as a template for PCR amplification using primers NPB29-6f (SEQ ID NO:28) and NPB29-7r (SEQ ID NO:29). The expected fragment was obtained and sequenced using the Big-Dye sequencing system. The *ebh*24-16d8 mutant was found to have one mutation resulting in a change in the amino acid sequence of the protein, arginine 67 is changed to glutamine. This change is an artifact of the mutagenesis procedure. The amino acid sequence of the mutant polypeptide encoded by SEQ ID NO:60 is SEQ ID NO:61.

The nucleic acid sequence of SEQ ID NO:62 encodes a mutant *ebh*24-16c11, which also exhibits improved bioconversion yield. This *S. rimosus* transformant, *ebh*24-16c11 identified in the screening of mutation 59 (primer NPB29mut59 (SEQ ID NO:70)) also produced a greater yield of epothilone F. Plasmid DNA was isolated from the *S. rimosus* culture and used as a template for PCR amplification using primers NPB29-6f (SEQ ID NO:28) and NPB29-7r (SEQ ID NO:29). The expected fragment was obtained and sequenced using the Big-Dye sequencing system. The *ebh*24-16c11 mutant was found to have two additional mutations resulting in changes in the amino acid sequence of the protein, alanine 93 is changed to glycine and isoleucine 365 is changed to threonine. The position 93 is the target of the mutagenesis, the change at 365 is an artifact of the mutagenesis procedure. The amino acid sequence of the mutant polypeptide encoded by SEQ ID NO:62 is depicted in SEQ ID NO:63.

The nucleic acid sequence of SEQ ID NO:64 encodes a mutant *ebh*24-16-16, which also exhibits improved bioconversion yield. This *S. rimosus* transformant, *ebh*24-16-16 identified in the screening of random mutants of *ebh*24-16 also produced a greater yield of epothilone F. Plasmid DNA was isolated from the *S. rimosus* culture and used as a template for PCR amplification using primers NPB29-6f (SEQ ID NO:28) and NPB29-7r (SEQ ID NO:29). The expected fragment was obtained and sequenced using the Big-Dye sequencing system. The *ebh*24-16-16 mutant was found to have one additional mutation resulting in changes in the amino acid sequence of the protein, valine 106 is changed to alanine. The amino acid sequence of the mutant polypeptide encoded by SEQ ID NO:64 is depicted in SEQ ID NO:65.

The nucleic acid sequence of SEQ ID NO:66 encodes a mutant *ebh*24-16-74, which also exhibits improved bioconversion yield. This *S. rimosus* transformant, *ebh*24-16-74 identified in the screening of random mutants of *ebh*24-16 also produced a greater yield of epothilone F. Plasmid DNA was isolated from the *S. rimosus* culture and used as a template for PCR amplification using primers NPB29-6f (SEQ ID NO:28) and NPB29-7r (SEQ ID NO:29). The expected fragment was obtained and sequenced using the Big-Dye sequencing system. The *ebh*24-16-74 mutant was found to have one additional mutation resulting in changes in the amino acid sequence of the protein, arginine 88 is changed to histidine. The amino acid sequence of the mutant polypeptide encoded by SEQ ID NO:66 is SEQ ID NO:67.

The nucleic acid sequence of SEQ ID NO:68 encodes a mutant *ebh*24-M18, which also exhibits improved bioconversion yield. This *S. rimosus* transformant, *ebh*M-18 identified in the screening of random mutants of *ebh* also produced a greater yield of epothilone F. Plasmid DNA was isolated from the *S. rimosus* culture and used as a template for PCR amplification using primers NPB29-6f (SEQ ID NO:28) and NPB29-7r (SEQ ID NO:29). The expected fragment was obtained and sequenced using the Big-Dye sequencing system. The *ebh*M-18 mutant was found to have two mutations resulting in changes in the amino acid sequence of the protein, glutamic acid 31 is changed to lysine and methionine 176 is changed to valine. The amino acid sequence of the mutant polypeptide encoded by SEQ ID NO:68 is depicted in SEQ ID NO:69.

The nucleic acid sequence of SEQ ID NO:72 encodes a mutant *ebh*24-16g8, which also exhibits improved bioconversion yield. This *S. rimosus* transformant, *ebh*24-16g8 identified in the screening of mutation 50 (primer NPB29mut50 (SEQ ID NO:71)) also produced a greater yield of epothilone F. Plasmid DNA was isolated from the *S. rimosus* culture and used as a template for PCR amplification using primers NPB29-6f (SEQ ID NO:28) and NPB29-7r (SEQ ID NO:29). The expected fragment was obtained and sequenced using the Big-Dye sequencing system. The *ebh*24-16g8 mutant was found to have two additional mutations resulting in changes in the amino acid sequence of the protein, methionine 176 is changed to alanine and isoleucine 130 is changed to threonine. The position 176 is the target of the mutagenesis, the change at 130 is an artifact of the mutagenesis procedure. The amino acid sequence of the mutant polypeptide encoded by SEQ ID NO:72 is depicted in SEQ ID NO:73.

The nucleic acid sequence of SEQ ID NO:74 encodes a mutant *ebh*24-16b9, which also exhibits improved bioconversion yield. This *S. rimosus* transformant, *ebh*24-16b9 identified in the screening of mutation 50 (primer NPB29mut50 (SEQ ID NO:71)) also produced a greater yield of epothilone F. Plasmid DNA was isolated from the *S. rimosus* culture and used as a template for PCR amplification using primers NPB29-6f (SEQ ID NO:28) and NPB29-7r (SEQ ID NO:29). The expected fragment was obtained and sequenced using the Big-Dye sequencing system. The *ebh*24-16b9 mutant was found to have two additional mutations resulting in changes

in the amino acid sequence of the protein, methionine 176 is changed to serine and alanine 140 is changed to threonine. The position 176 is the target of the mutagenesis, the change at 140 is an artifact of the mutagenesis procedure. The amino acid sequence of the mutant polypeptide encoded by SEQ ID NO:74 is depicted in SEQ ID NO:75.

A mixture composed of the plasmids pANT849*ebh*-24-16, pANT849*ebh*-10-53, pANT849*ebh*-24-16d8, pANT849*ebh*-24-16c11, pANT849*ebh*-24-16-16, pant849*ebh*-24-16-74, pANT849*ebh*-24-16b9, pANT849*ebh*-M18 and pANT849*ebh*-24-16g8 for these nine mutant genes was deposited and accepted by an International Depository Authority under the provisions of the Budapest Treaty. The deposit was made on November 21, 2002 to the American Type Culture Collection at 10801 University Boulevard in Manassas, Virginia 20110-2209. The ATCC Accession Number is PTA-4808. All restrictions upon public access to this mixture of plasmids will be irrevocably removed upon granting of this patent application. The deposit will be maintained in a public depository for a period of thirty years after the date of deposit or five years after the last request for a sample or for the enforceable life of the patent, whichever is longer. The above-referenced mixture of plasmids was viable at the time of the deposit. The deposit will be replaced if viable samples cannot be dispensed by the depository.

Thus, in accordance with another aspect of the present invention, there are provided isolated polypeptides of epothilone B hydroxylase and variants and mutants thereof and isolated polypeptides of ferredoxin or variants thereof. In one embodiment of the present invention, by "polypeptide" it is meant to include the amino acid sequence of SEQ ID NO: 2, and fragments or variants, which retain essentially the same biological activity and/or function as this epothilone B hydroxylase. In another embodiment of the present invention, by "polypeptide" it is meant to include the amino acid sequence of SEQ ID NO:4, and fragments and/or variants, which retain essentially the same biological activity and/or function as this ferredoxin.

By "variants" as used herein it is meant to include polypeptides with amino acid sequences with conservative amino acid substitutions as compared to SEQ ID NO: 2 or 4 which are demonstrated to exhibit similar biological activity and/or

function to SEQ ID NO:2 or 4. By "conservative amino acid substitutions" it is meant to include replacement, one for another, of the aliphatic amino acids such as Ala, Val, Leu and Ile, the hydroxyl residues Ser and Thr, the acidic residues Asp and Glu, and the amide residues Asn and Gln. Exemplary variant amino acid sequences of the present invention are depicted in SEQ ID NO:43-49 and the amino acid substitutions of these exemplary variants are described in Table 2, *supra*.

By "mutants" as used herein it is meant to include polypeptides encoded by nucleic acid sequences with one or more point mutations, or deletions or additions of nucleic acids as compared to SEQ ID NO: 1 or 3, but which still have similar activity to the polypeptides encoded by SEQ ID NO: 1 or 3. In a preferred embodiment, mutations are made to the nucleic acid that alter the substrate specificity and/or yield from the polypeptide encoded thereby. A preferred region of mutation with respect to the epothilone B hydroxylase gene is that region of the nucleic acid sequence coding for the approximately 113 amino acid residues comprising the active site of the enzyme. Also preferred are mutants with at least one amino acid substitution at amino acid position GLU31, ARG67, ARG88, ILE92, ALA93, VAL106, ILE130, ALA140, MET176, PHE190, GLU 231, SER294, PHE237, or ILE365 of SEQ ID NO:1 Exemplary mutants *ebh*25-1, *ebh*10-53, *ebh*24-16, *ebh*24-16d8, *ebh*24-16c11, *ebh*24-16-16, *ebh*24-16-74, *ebh*24-16g8, *ebh*24-16b9 and the nucleic acid sequences encoding such mutants of the present invention are depicted in SEQ ID NO:31, 33, 35, 61, 63, 65, 67, 69, 71, 73 and 75, and SEQ ID NO:30, 32, 34, 60, 62, 64, 66, 68, 70, 72 and 74, respectively.

A 3-dimensional model of epothilone B hydroxylase has also been constructed in accordance with general teachings of Greer et al. (Comparative modeling of homologous proteins. Methods In Enzymology 202239-52, 1991), Lesk et al. (Homology Modeling: Inferences from Tables of Aligned Sequences. Curr. Op. Struc. Biol. (2) 242-247, 1992), and Cardozo et al. (Homology modeling by the ICM method. Proteins 23, 403-14, 1995) on the basis of the known structure of a homologous protein EryF (PDB Code 1KIN chain A). Homology between these sequences is 34%. Alignment of the sequences of epothilone B hydroxylase (SEQ ID NO:2) and EryF (PDB Code 1KIN chain A; SEQ ID NO:76) is depicted in Figure 3.

A homology model of epothilone B hydroxylase based upon sequence alignment with EryF is depicted in Figure 4.

An energy plot of the epothilone B hydroxylase model relative to EryF (PDB code 1JIN) was also prepared and is depicted in Figure 5. An averaging window size of 51 residues was used at a given residue position to calculate the average of the energies of the 51 residues in the sequence that lie with the given residue at the central position. As shown in Figure 5, all energies along the sequence lie below zero thus indicating that the modeled structure as set forth in Figure 4 and Appendix 1 is reasonable.

The three-dimensional structure represented in the homology model of epothilone B hydroxylase of Figure 4 is defined by a set of structure coordinates as set forth in Appendix 1. The term "structure coordinates" refers to Cartesian coordinates generated from the building of a homology model. As will be understood by those of skill in the art, however, a set of structure coordinates for a protein is a relative set of points that define a shape in three dimensions. Thus, it is possible that an entirely different set of coordinates could define a similar or identical shape. Moreover, slight variations in the individual coordinates, as emanate from generation of similar homology models using different alignment templates and/or using different methods in generating the homology model, will have minor effects on the overall shape. Variations in coordinates may also be generated because of mathematical manipulations of the structure coordinates. For example, the structure coordinates set forth in Appendix 1 could be manipulated by fractionalization of the structure coordinates; integer additions or subtractions to sets of the structure coordinates, inversion of the structure coordinates or any combination of the above.

Various computational analyses are therefore necessary to determine whether a molecule or a portion thereof is sufficiently similar to all or parts of epothilone B hydroxylase described above as to be considered the same. Such analyses may be carried out in current software applications, such as SYBYL version 6.7 or INSIGHTII (Molecular Simulations Inc., San Diego, CA) version 2000 and as described in the accompanying User's Guides.

For example, the superimposition tool in the program SYBYL allows comparisons to be made between different structures and different conformations of

the same structure. The procedure used in SYBYL to compare structures is divided into four steps: 1) load the structures to be compared; 2) define the atom equivalencies in these structures; 3) perform a fitting operation; and 4) analyze the results. Each structure is identified by a name. One structure is identified as the target (i.e., the fixed structure); the second structure (i.e., moving structure) is identified as the source structure. Since atom equivalency within SYBYL is defined by user input, for the purpose of this aspect of the present invention equivalent atoms are defined as protein backbone atoms (N, Cα, C and O) for all conserved residues between the two structures being compared. Further, only rigid fitting operations are considered . When a rigid fitting method is used, the working structure is translated and rotated to obtain an optimum fit with the target structure. The fitting operation uses an algorithm that computes the optimum translation and rotation to be applied to the moving structure, such that the root mean square difference of the fit over the specified pairs of equivalent atoms is an absolute minimum. This number, given in angstroms, is reported by SYBYL.

For the purposes of the present invention, any homology model of epothilone B hydroxylase that has a root mean square deviation of conserved residue backbone atoms (N, Cα, C, O) of less than about 4.0 Å when superimposed on the corresponding backbone atoms described by structure coordinates listed in Appendix 1 are considered identical. More preferably, the root mean square deviation is less than about 3.0 Å. More preferably the root mean square deviation is less than about 2.0 Å.

For the purpose of this invention, any homology model of epothilone B hydroxylase that has a root mean square deviation of conserved residue backbone atoms (N, Cα, C, O) of less than about 2.0 Å when superimposed on the corresponding backbone atoms described by structure coordinates listed in Appendix 1 are considered identical. More preferably, the root mean square deviation is less than about 1.0 Å.

In another embodiment of the present invention, structural models wherein backbone atoms have been substituted with other elements which when superimposed on the corresponding backbone atoms have low root mean square deviations are considered to be identical. For example, an homology model where the original

backbone carbon, and/or nitrogen and/or oxygen atoms are replaced with other elements having a root mean square deviation of about 4.0 Å, more preferably about 3.0 Å, even more preferably less than about 2Å, when superimposed on the corresponding backbone atoms described by structure coordinates listed in Appendix 1 is considered identical.

The term "root mean square deviation" means the square root of the arithmetic mean of the squares of the deviations from the mean. It is a way to express the deviation or variation from a trend or object. For purposes of this invention, the "root mean square deviation" defines the variation in the backbone of a protein from the relevant portion of the backbone of the epothilone B hydroxylase portion of the complex as defined by the structure coordinates described herein.

The present invention as embodied by the homology model enables the structure-based design of additional mutants of epothilone B hydroxylase. For example, using the homology model of the present invention, residues lying within 10Å of the binding site of epothilone B hydroxylase have now been defined. These residues include LEU39, GLN43, ALA45, MET57, LEU58, HIS62, PHE63, SER64, SER65, ASP66, ARG67, GLN68, SER69, LEU74, MET75, VAL76, ALA77, ARG78, GLN79, ILE80, ASP84, LYS85, PRO86, PHE87, ARG88, PRO89, SER90, LEU91, ILE92, ALA93, MET94, ASP95, HIS99, ARG103, PHE110, ILE155, PHE169, GLN170, CYS172, SER173, SER174, ARG175, MET176, LEU177, SER178, ARG179, ARG186, PHE190, LEU193, VAL233, GLY234, LEU235, ALA236, PHE237, LEU238, LEU239, LEU240, ILE241, ALA242, GLY243, HIS244, GLU245, THR246, THR247, ALA248, ASN249, MET250, LEU283, THR287, ILE288, ALA289, GLU290, THR291, ALA292, THR293, SER294, ARG295, PHE296, ALA297, THR298, GLU312, GLY313, VAL314, VAL315, GLY316, VAL344, ALA345, PHE346, GLY347, PHE348, VAL350, HIS351, GLN352, CYS353, LEU354, GLY355, GLN356, LEU358, ALA359, GLU362, LYS389, ASP391, SER392,THR393, ILE394 and TYR395 as set forth in Appendix 1. Mutants with mutations at one or more of these positions are expected to exhibit altered biological function and/or specificity and thus comprise another embodiment of preferred mutants of the present invention. Another embodiment of preferred

mutants are molecules that have a root mean square deviation from the backbone atoms of said epothilone B hydroxylase of not more than about 4.0Å.

The structure coordinates of an epothilone B hydroxylase homology model or portions thereof are stored in a machine-readable storage medium. Such data may be used for a variety of purposes, such as drug discovery.

Accordingly, another aspect of the present invention relates to machine-readable data storage medium comprising a data storage material encoded with the structure coordinates set forth in Appendix 1.

The three-dimensional model structure of epothilone B hydroxylase can also be used to identify modulators of biological function and potential substrates of the enzyme. Various methods or combinations thereof can be used to identify such modulators.

For example, a test compound can be modeled that fits spatially into a binding site in epothilone B hydroxylase, according to Appendix 1. Structure coordinates of amino acids within 10 Å of the binding region of epothilone B hydroxylase defined by amino acids LEU39, GLN43, ALA45, MET57, LEU58, HIS62, PHE63, SER64, SER65, ASP66, ARG67, GLN68, SER69, LEU74, MET75, VAL76, ALA77, ARG78, GLN79, ILE80, ASP84, LYS85, PRO86, PHE87, ARG88, PRO89, SER90, LEU91, ILE92, ALA93, MET94, ASP95, HIS99, ARG103, PHE110, ILE155, PHE169, GLN170, CYS172, SER173, SER174, ARG175, MET176, LEU177, SER178, ARG179, ARG186, PHE190, LEU193, VAL233, GLY234, LEU235, ALA236, PHE237, LEU238, LEU239, LEU240, ILE241, ALA242, GLY243, HIS244, GLU245, THR246, THR247, ALA248, ASN249, MET250, LEU283, THR287, ILE288, ALA289, GLU290, THR291, ALA292, THR293, SER294, ARG295, PHE296, ALA297, THR298, GLU312, GLY313, VAL314, VAL315, GLY316, VAL344, ALA345, PHE346, GLY347, PHE348, VAL350, HIS351, GLN352, CYS353, LEU354, GLY355, GLN356, LEU358, ALA359, GLU362, LYS389, ASP391, SER392,THR393, ILE394 and TYR395, and the coordinated heme group, HEM1 can also be used to identify desirable structural and chemical features of such modulators. Identified structural or chemical features can then be employed to design or select compounds as potential epothilone B hydroxylase ligands. By structural and chemical features it is meant to include, but is not limited

to, covalent bonding, van der Waals interactions, hydrogen bonding interactions, charge interaction, hydrophobic bonding interaction, and dipole interaction. Compounds identified as potential epothilone B hydroxylase ligands can then be synthesized and screened in an assay characterized by binding of a test compound to epothilone B hydroxylase, or in characterizing the ability of epothilone B hydroxylase to modulate a protease target in the presence of a small molecule. Examples of assays useful in screening of potential epothilone B hydroxylase ligands include, but are not limited to, screening in silico, *in vitro* assays and high throughput assays.

As will be understood by those of skill in the art upon this disclosure, other structure-based design methods can be used. Various computational structure-based design methods have been disclosed in the art. For example, a number of computer modeling systems are available in which the sequence of epothilone B hydroxylase and the epothilone B hydroxylase structure (i.e., atomic coordinates of epothilone B hydroxylase as provided in Appendix 1 and/or the atomic coordinates within 10Å of the binding region as provided above) can be input. This computer system then generates the structural details of one or more these regions in which a potential epothilone B hydroxylase modulator binds so that complementary structural details of the potential modulators can be determined. Design in these modeling systems is generally based upon the compound being capable of physically and structurally associating with epothilone B hydroxylase. In addition, the compound must be able to assume a conformation that allows it to associate with epothilone B hydroxylase. Some modeling systems estimate the potential inhibitory or binding effect of a potential epothilone B hydroxylase substrate or modulator prior to actual synthesis and testing.

Methods for screening chemical entities or fragments for their ability to associate with a given protein target are also well known. Often these methods begin by visual inspection of the binding site on the computer screen. Selected fragments or chemical entities are then positioned in a binding region of epothilone B hydroxylase. Docking is accomplished using software such as INSIGHTII, QUANTA and SYBYL, following by energy minimization and molecular dynamics with standard molecular mechanic force fields such as, MMFF, CHARMM and AMBER. Examples of computer programs which assist in the selection of chemical fragment or chemical

entities useful in the present invention include, but are not limited to, GRID (Goodford, 1985), AUTODOCK (Goodsell, 1990), and DOCK (Kuntz et al. 1982).

Upon selection of preferred chemical entities or fragments, their relationship to each other and epothilone B hydroxylase can be visualized and then assembled into a single potential modulator. Programs useful in assembling the individual chemical entities include, but are not limited to CAVEAT (Bartlett et al. 1989) and 3D Database systems (Martin 1992).

Alternatively, compounds may be designed *de novo* using either an empty active site or optionally including some portion of a known inhibitor. Methods of this type of design include, but are not limited to LUDI (Bohm 1992) and LeapFrog (Tripos Inc., St. Louis MO).

Programs such as DOCK (Kuntz et al. 1982) can be used with the atomic coordinates from the homology model to identify potential ligands from databases or virtual databases which potentially bind the in the active site binding region which may therefore be suitable candidates for synthesis and testing.

Also provided in the present invention are vectors comprising polynucleotides of the present invention and host cells which are genetically engineered with vectors of the present invention to produce epothilone B hydroxylase or active fragments and variants or mutants of this enzyme and/or ferredoxin or active fragments thereof. Generally, any vector suitable to maintain, propagate or express polynucleotides to produce these polypeptides in the host cell may be used for expression in this regard. In accordance with this aspect of the invention the vector may be, for example, a plasmid vector, a single- or double-stranded phage vector, or a single- or double-stranded RNA or DNA viral vector. Vectors may be extra-chromosomal or designed for integration into the host chromosome. Such vectors include, but are not limited to, chromosomal, episomal and virus-derived vectors e.g., vectors derived from bacterial plasmids, bacteriophages, yeast episomes, yeast chromosomal elements, and viruses such as baculoviruses, papova viruses, SV40, vaccinia viruses, adenoviruses, fowl pox viruses, pseudorabies viruses and retroviruses, and vectors derived from combinations thereof, such as those derived from plasmid and bacteriophage genetic elements, cosmids and phagemids.

Useful expression vectors for prokaryotic hosts include, but are not limited to, bacterial plasmids, such as those from *E. coli*, *Bacillus* or *Streptomyces*, including pBluescript, pGEX-2T, pUC vectors, pET vectors, ColE1, pCR1, pBR322, pMB9, pCW, pBMS200, pBMS2020, PIJ101, PIJ702, pANT849, pOJ260, pOJ446, pSET152, pKC1139, pKC1218, pFD666 and their derivatives, wider host range plasmids, such as RP4, phage DNAs, *e.g.*, the numerous derivatives of phage lambda, *e.g.*, NM989, λGT10 and λGT11, and other phages, *e.g.*, M13 and filamentous single stranded phage DNA.

Vectors of the present invention for use in yeast will typically contain an origin of replication suitable for use in yeast and a selectable marker that is functional in yeast. Examples of yeast vectors useful in the present invention include, but are not limited to, Yeast Integrating plasmids (*e.g.*, YIp5) and Yeast Replicating plasmids (the YRp and YEp series plasmids), Yeast Centromere plasmids (the YCp series plasmids), Yeast Artificial Chromosomes (YACs) which are based on yeast linear plasmids, denoted YLp, pGPD-2, 2μ plasmids and derivatives thereof, and improved shuttle vectors such as those described in Gietz *et al.*, *Gene*, 74: 527-34 (1988) (YIplac, YEplac and YCplac).

Mammalian vectors useful for recombinant expression may include a viral origin, such as the SV40 origin (for replication in cell lines expressing the large T-antigen, such as COS1 and COS7 cells), the papillomavirus origin, or the EBV origin for long term episomal replication (for use, *e.g.*, in 293-EBNA cells, which constitutively express the EBV EBNA-1 gene product and adenovirus E1A). Expression in mammalian cells can be achieved using a variety of plasmids, including, but not limited to, pSV2, pBC12BI, and p91023, pCDNA vectors as well as lytic virus vectors (*e.g.*, vaccinia virus, adeno virus, and baculovirus), episomal virus vectors (*e.g.*, bovine papillomavirus), and retroviral vectors (*e.g.*, murine retroviruses). Useful vectors for insect cells include baculoviral vectors and pVL941.

Selection of an appropriate promoter to direct mRNA transcription and construction of expression vectors are well known. In general, however, expression constructs will contain sites for transcription initiation and termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the mature transcripts expressed by the constructs will include a translation initiating

codon at the beginning and a termination codon appropriately positioned at the end of the polypeptide to be translated.

Examples of useful promoters for prokaryotes include, but are not limited to phage promoters such as phage lambda pL promoter, the trc promoter, a hybrid derived from the trp and lac promoters, the bacteriophage T7 promoter, the TAC or TRC system, the major operator and promoter regions of phage lambda, the control regions of fd coat protein, *snp*A promoter, *mel*C promotor, *erm*E* promoter or the *ara*BAD operon. Examples of useful promoters for yeast include, but are not limited to, the CYC1 promoter, the GAL1 promoter, the GAL10 promoter, ADH1 promoter, the promoters of the yeast α-mating system, and the GPD promoter. Examples of promoters routinely used in mammalian expression vectors include, but are not limited to, the CMV immediate early promoter, the HSV thymidine kinase promoter, the early and late SV40 promoters, the promoters of retroviral LTRs, such as those of the Rous Sarcoma Virus(RSV), and metallothionein promoters, such as the mouse metallothionein-I promoter.

Vectors comprising the polynucleotides can be introduced into host cells using any number of well known techniques including infection, transduction, transfection, transvection and transformation. The polynucleotides may be introduced into a host alone or with additional polynucleotides encoding, for example, a selectable marker or ferredoxin reductase. In a preferred embodiment of the present invention the polynucleotide for epothilone B hydroxylase and ferredoxin are introduced into the host cell. Host cells for the various expression constructs are well known, and those of skill can routinely select a host cell for expressing the epothilone B hydroxylase and/or ferredoxin in accordance with this aspect of the present invention. Examples of mammalian expression systems useful in the present invention include, but are not limited to, the C127, 3T3, CHO, HeLa, human kidney 293 and BHK cell lines, and the COS-7 line of monkey kidney fibroblasts.

Alternatively, as exemplified herein, epothilone B hydroxylase and ferredoxin can be expressed recombinantly in microorganisms.

Accordingly, another aspect of the present invention relates to recombinantly produced microorganisms which express epothilone B hydroxylase alone or in conjunction with the ferredoxin and which are capable of hydroxylating a compound ,

and in particular an epothilone, having a terminal alkyl group to produce ones having a terminal hydroxyalkyl group. The recombinantly produced microorganisms are produced by transforming cells such as bacterial cells with a plasmid comprising a nucleic acid sequence encoding epothilone B hydroxylase. In a preferred embodiment, the cells are transformed with a plasmid comprising a nucleic acid encoding epothilone B hydroxylase or mutants or variants thereof as well as the nucleic acid sequence encoding ferredoxin located downstream of the epothilone B hydroxylase gene. Examples of microorganisms which can be transformed with these plasmids to produce the recombinant microorganisms of the present invention include, but are not limited, *Escherichia coli, Bacillus megaterium, Amycolatopsis orientalis, Sorangium cellulosum, Rhodococcus erythropolis,* and *Streptomyces species* such as *Streptomyces lividans, Streptomyces virginiae, Streptomyces venezuelae, Streptomyces albus, Streptomyces coelicolor, Streptomyces rimosus* and *Streptomyces griseus.*

The recombinantly produced microorganisms of the present invention are useful in microbial processes or methods for production of compounds, and in particular epothilones, containing a terminal hydroxyalkyl group. In general, the hydroxyalkyl-bearing product can be produced by culturing the recombinantly produced microorganism or enzyme derived therefrom, capable of selectively hydroxylating a terminal carbon or alkyl, in the presence of a suitable substrate in an aqueous nutrient medium containing sources of assimilable carbon and nitrogen, under submerged aerobic conditions.

Suitable epothilones employed as substrate for the method of the present invention may be any such compound having a terminal carbon or terminal alkyl group capable of undergoing the enzymatic hydroxylation of the present invention. The starting material, or substrate, can be isolated from natural sources, such as *Sorangium cellulosum*, or they can be synthetically formed epothilones. Other substrates having a terminal carbon or terminal alkyl group capable of undergoing an enzymatic hydroxylation can be employed by the methods herein. For example, compactin can be used as a substrate, which upon hydroxylation forms the compound pravastatin. Methods for hydroxylating compactin to pravastatin via an *Actinomadura* strain are set forth in U.S. Patent 5,942,423 and U.S. Patent 6,274,360.

For example, using the recombinant microorganisms of the present invention at least one epothilone can be prepared as described in WO 00/39276, U. S. Serial. No. 09/468,854, filed December 21, 1999, the text of which is incorporated herein as if set forth at length. An epothilone of the following Formula I

$$HO\text{-}CH_2\text{-}(A_1)_n\text{-}(Q)_m\text{-}(A_2)_o\text{-}E \qquad (I)$$

where

A_1 and A_2 are independently selected from the group of optionally substituted C_1-C_3 alkyl and alkenyl;

Q is an optionally substituted ring system containing one to three rings and at least one carbon to carbon double bond in at least one ring;

n, m, and o are integers selected from the group consisting of zero and 1, where at least one of m or n or o is 1; and

E is an epothilone core; can be prepared.

This method comprises the steps of contacting at least one epothilone of the following formula II

$$CH_3\text{-}(A_1)_n\text{-}(Q)_m\text{-}(A_2)_o\text{-}E \qquad (II)$$

where A_1, Q, A_2, E, n, m, and o are defined as above;

with a recombinantly produced microorganism, or an enzyme derived therefrom, which is capable of selectively catalyzing the hydroxylation of formula II, and effecting said hydroxylation.

In a preferred embodiment, the starting material is epothilone B. Epothilone B can be obtained from the fermentation of *Sorangium cellulosum* So ce90, as described in DE 41 38 042 and WO 93/10121. The strain has been deposited at the Deutsche Sammlung von Mikroorganismen (German Collection of Microorganisms) (DSM) under No. 6773. The process of fermentation is also described in Hofle, G., et al., *Angew. Chem. Int. Ed. Engl.,* Vol 35, No. 13/14, 1567-1569 (1996). Epothilone B can also be obtained by chemical means, such as those disclosed by Meng, D., et al., *J. Am. Chem. Soc.*, Vol. 119, No. 42, 10073-10092 (1996); Nicolaou, K., et al., *J. Am. Chem. Soc.*, Vol. 119, No. 34, 7974-7991 (1997) and Schinzer, D., et al., *Chem. Eur. J.*, Vol. 5, No. 9, 2483-2491 (1999).

Growth of the recombinantly produced microorganism selected for use in the process may be achieved by one of ordinary skill in the art by the use of appropriate

nutrient medium. Appropriate media for the growing of the recombinantly produced microorganisms include those that provide nutrients necessary for the growth of microbial cells. See, for example, T. Nagodawithana and J. M. Wasileski, Chapter 2: "Media Design for Industrial Fermentations," Nutritional Requirements of Commercially Important Microorganism, edited by T. W. Nagodawithana and G. Reed, Esteekay Associates, Inc., Milwaukee, WI, 18-45 (1998); T. L. Miller and B. W. Churchill, Chapter 10: "Substrates for Large-Scale Fermentations," Manual of Industrial Microbiology and Biotechnology, edited by A.L. Demain and N. A. Solomon, American Society for Microbiology, Washington, D.C., 122-136 (1986). A typical medium for growth includes necessary carbon sources, nitrogen sources, and trace elements. Inducers may also be added to the medium. The term inducer as used herein, includes any compound enhancing formation of the desired enzymatic activity within the recombinantly produced microbial cell. Typical inducers as used herein may include solvents used to dissolve substrates, such as dimethyl sulfoxide, dimethyl formamide, dioxane, ethanol and acetone. Further, some substrates, such as epothilone B, may also be considered to be inducers.

Carbon sources may include sugars such as glucose, fructose, galactose, maltose, sucrose, mannitol, sorbital, glycerol starch and the like; organic acids such as sodium acetate, sodium citrate, and the like; and alcohols such as ethanol, propanol and the like. Preferred carbon sources include, but are not limited to, glucose, fructose, sucrose, glycerol and starch.

Nitrogen sources may include an N-Z amine A, corn steeped liquor, soybean meal, beef extract, yeast extract, tryptone, peptone, cottonseed meal, peanut meal, amino acids such as sodium glutamate and the like, sodium nitrate, ammonium sulfate and the like.

Trace elements may include magnesium, manganese, calcium, cobalt, nickel, iron, sodium and potassium salts. Phosphates may also be added in trace or preferably, greater than trace amounts.

The medium employed for the fermentation may include more than one carbon or nitrogen source or other nutrient.

For growth of the recombinantly produced microorganisms and/or hydroxylation according to the method of the present invention, the pH of the medium

is preferably from about 5 to about 8 and the temperature is from about 14°C to about 37°C, preferably the temperature is 28°C. The duration of the reaction is 1 to 100 hours, preferably 8 to 72 hours.

The medium is incubated for a period of time necessary to complete the biotransformation as monitored by high performance liquid chromatography (HPLC). Typically, the period of time needed to complete the transformation is twelve to one hundred hours and preferably about 72 hours after the addition of the substrate. The medium is placed on a rotary shaker (New Brunswick Scientific Innova 5000) operating at 150 to 300 rpm and preferably about 250 rpm with a throw of 2 inches.

The hydroxyalkyl-bearing product can be recovered from the fermentation broth by conventional means that are commonly used for the recovery of other known biologically active substances. Examples of such recovery means include, but are not limited to, isolation and purification by extraction with a conventional solvent, such as ethyl acetate and the like; by pH adjustment; by treatment with a conventional resin, for example, by treatment with an anion or cation exchange resin or a non-ionic adsorption resin; by treatment with a conventional adsorbent, for example, by distillation, by crystallization; or by recrystallization, and the like.

The extract obtained above from the biotransformation reaction mixture can be further isolated and purified by column chromatography and analytical thin layer chromatography.

The ability of a recombinantly produced microorganism of the present invention to biotransform an epothilone having a terminal alkyl group to an epothilone having a terminal hydroxyalkyl group was demonstrated. In these experiments, a culture comprising a *Streptomyces lividans* clone containing a plasmid with the *ebh* gene as described in more detail in Example 11 was incubated with an epothilone B suspension for 3 days at 30°with agitation. A sample of the incubate was extracted with an equal volume of 25% methanol: 75% n-butanol, vortexed and allowed to settle for 5 minutes. Two hundred µl of the organic phase was transferred to an HPLC vial and analyzed by HPLC/MS (Example 12). A product peak of epothilone F eluted at a retention time of 15.9 minutes and had a protonated molecular weight of 524. The epothilone B substrate eluted at 19.0 minutes and had a

protonated molecular weight of 508. The peak retention times and molecular weights were confirmed using known standards.

Rates of biotransformation of epothilone B by cells expressing *ebh* were also compared to rates of biotransformation by *ebh* mutants. Cells expressing *ebh* comprised a frozen spore preparation of. *S. lividans* (pANT849-*ebh*). Cells expressing mutants comprises frozen spore preparations of *S. lividans* (pANT849-*ebh*10-53) and *S. lividans* (pANT849-*ebh*24-16). A frozen spore preparation of *S. lividans* TK24 was used as the control. The cells were pre-incubated for several days at 30°C. Following this pre-incubation, epothilone B in 100% EtOH was added to each culture to a final concentration of 0.05% weight/volume. Samples were then taken at 0, 24, 48 and 72 hours with the exception of the *S. lividans* (pANT849-*ebh*24-16) culture, in which the epothilone B had been completely converted to epothilone F at 48 hours. The samples were analyzed by HPLC. The results are calculated as a percentage of the epothilone B at time 0 hours.

Epothilone B:

Time (hours)	TK24	pANT849-*ebh*	pANT849-*ebh*10-53	pANT849-*ebh*24-16
0	100%	100%	100%	100%
24	99%	78%	69%	56%
48	87%	19%	39%	0%
72	87%	0%	3%	---

Epothilone F:

Time (hours)	TK24	pANT849-*ebh*	pANT849-*ebh*10-53	pANT849-*ebh*24-16
0	0%	0%	0%	0%
24	0%	4%	9%	23%
48	0%	21%	29%	52%
72	0%	14%	41%	---

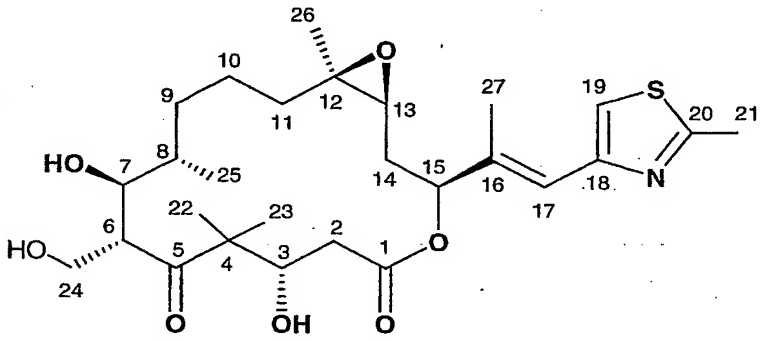
The ability of cells expressing *ebh* to biotransform compactin to pravastatin was also examined. In these experiments, frozen spore preparations of *S. lividans* (pANT849) or *S. lividans* (pANT849-*ebh*) were grown for several days at 30°C.

Following the pre-incubation, an aliquot of each cell culture was transferred to a polypropylene culture tube, compactin was added to each culture tube, and the tubes were incubated for 24 hours, 30°C, 250 rpm. An aliquot of the culture broth was then extracted and compactin and pravastatin values relative to the control *S. lividans* (pANT849) culture were measured via HPLC.

Compactin and pravastatin as a percentage of starting compactin concentration:

	S. lividans (pANT849)	*S. lividans* (pANT849-*ebh*)
Compactin	36%	11%
Pravastatin	11%	53%

As discussed *supra*, mutant *ebh*25-1 (SEQ ID NO:30) exhibits altered substrate specificity and biotransformation of epothilone B by this mutant resulted in a product with a different HPLC elution time than epothilone B or epothilone F. A sample of this unknown was analyzed by LC-MS and was found to have a molecular weight of 523 (M.W.), consistent with a single hydroxylation of epothilone B. The structure of the biotransformation product was determined as 24-hydroxyl-epothilone B, based on MS and NMR data (compared with data of epothilone B):



24-hydroxyl-epothilone B

Formula A

Molecular Formula:	$C_{27}H_{41}NO_7S$
Molecular Weight:	523
Mass Spectrum:	ES+ (m/z): 524($[M+H]^+$), 506.
LC/MS/MS:	+ESI (m/z): 524, 506, 476, 436, 320
HRMS:	Calculated for $[M+H]^+$: 524.2682; Found: 524.2701

HPLC (Rt)	7.3 minutes (on the analytical HPLC system)
LC/NMR	Observed Chemical Shifts
	Varian AS-600 (Proton: 599.624 MHz),
	Solvent D_2O/CD_3CN (δ 1.94): ~4/6
	Proton: δ7.30 (s, 1H), 6.43 (s, 1H), 5.30 (m, 1H), 4.35 (m, 1H), 3.81 (m, 1H), 3.74 (m, 1H), 3.68 (m, 1H), 3.43 (m, 1H), 2.87 (m, 1H), 2.66 (s, 3H), 2.40 (m, 2H), 1.58 (b, 1H), 1.48 (b, 1H), 1.35 (m, 3H), 1.18 (s, 3H), 1.13 (s, 3H), 0.87 (m, 6H)
	*Peaks between 1.8-2.1 ppm were not observed due to solvent suppression.

The proton chemical shift was assigned as follows:

Position	Proton	Pattern
1	--	
2	2.40	m
3	4.35	m
4	--	
5	--	
6	3.43	m
7	3.68	m
8	1.58	m
9	1.35	b
10	1.48	b
10	1.35	b
11	SSP	
12	--	
13	2.87	m
14	SSP	
15	5.30	m
16	--	
17	6.43	s
18	--	

19	7.30	s
20	--	
21	2.66	s
22	1.18	s
23	0.87	m
24	3.81	m
24	3.74	m
25	0.87	m
26	1.13	s
27	SSP	

*SSP: no observed due to solvent suppression.

Accordingly, the compositions and methods of the present invention are useful in producing known compounds that are microtubule-stabilizing agents as well as new compounds comprising epothilone analogs such as 24-hydroxyl-epothilone B (Formula A) and pharmaceutically acceptable salts thereof expected to be useful as microtubule-stabilizing agents. The microtubule stabilizing agents produced using these compositions and methods are useful in the treatment of a variety of cancers and other proliferative diseases including, but not limited to, the following;

- carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, ovary, pancreas, stomach, cervix, thyroid and skin; including squamous cell carcinoma;
- hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burketts lymphoma;
- hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias and promyelocytic leukemia;
- tumors of mesenchymal origin, including fibrosarcoma and rhabdomyoscarcoma;
- other tumors, including melanoma, seminoma, tetratocarcinoma, neuroblastoma and glioma;

- tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma, and schwannomas;
- tumors of mesenchymal origin, including fibrosarcoma, rhabdomyosarcoma, and osteosarcoma; and
- other tumors, including melanoma, xenoderma pigmentosum, keratoactanthoma, seminoma, thyroid follicular cancer and teratocarcinoma.

Microtubule stabilizing agents produced using the compositions and methods of the present invention will also inhibit angiogenesis, thereby affecting the growth of tumors and providing treatment of tumors and tumor-related disorders. Such anti-angiogenesis properties of these compounds will also be useful in the treatment of other conditions responsive to anti-angiogenesis agents including, but not limited to, certain forms of blindness related to retinal vascularization, arthritis, especially inflammatory arthritis, multiple sclerosis, restinosis and psoriasis.

Microtubule stabilizing agents produced using the compositions and methods of the present invention will induce or inhibit apoptosis, a physiological cell death process critical for normal development and homeostasis. Alterations of apoptotic pathways contribute to the pathogenesis of a variety of human diseases. Compounds of the present invention such as those set forth in formula I and II and Formula A, as modulators of apoptosis, will be useful in the treatment of a variety of human diseases with aberrations in apoptosis including, but not limited to, cancer and precancerous lesions, immune response related diseases, viral infections, degenerative diseases of the musculoskeletal system and kidney disease.

Without wishing to be bound to any mechanism or morphology, microtubule stabilizing agents produced using the compositions and methods of the present invention may also be used to treat conditions other than cancer or other proliferative diseases. Such conditions include, but are not limited to viral infections such as herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus; autoimmune diseases such as systemic lupus erythematosus, immune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel diseases and autoimmune diabetes mellitus; neurodegenerative disorders such as Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration; AIDS; myelodysplastic

syndromes; aplastic anemia; ischemic injury associated myocardial infarctions; stroke and reperfusion injury; restenosis; arrhythmia; atherosclerosis; toxin-induced or alcohol induced liver diseases; hematological diseases such as chronic anemia and aplastic anemia; degenerative diseases of the musculoskeletal system such as osteoporosis and arthritis; aspirin-sensitive rhinosinusitis; cystic fibrosis; multiple sclerosis; kidney diseases; and cancer pain.

The following nonlimiting examples are provided to further illustrate the present invention.

EXAMPLES

Example 1: Reagents

R2 Medium was prepared as follows:

A solution containing sucrose (103 grams), K_2SO_4 (0.25 grams) $MgCl_2 \bullet 6H_2O$ (10.12 grams), glucose (10 grams), Difco Casaminoacids (0.1 grams) and distilled water (800 ml) was prepared. Eighty ml of this solution was then poured into a 200 ml screw capped bottle containing 2.2 grams Difco Bacto agar. The bottle was capped and autoclaved. At time of use, the medium was remelted and the following autoclaved solutions were added in the order listed:

1 ml KH_2PO_4 (0.5%)

8 ml $CaCl_2 \bullet 2H_2O$ (3.68%)

1.5 ml L-proline (20%)

10 ml TES buffer (5.73%, adjusted to pH 7.2)

0.2 ml Trace element solution containing $ZnCl_2$(40mg), $FeCl_3 \bullet 6H_2O$(200 mg), $CuCl_2 \bullet 2H_2O$ (10 mg), $MnCl_2 \bullet 4H_2O$ (10 mg), $Na_2B_4O_7 \bullet 10H_2O$ (10 mg), and $(NH_4)_6Mo_7O_{24} \bullet H_2O$

0.5 ml NaOH (1N)(sterilization not required)

0.5 ml Required growth factors for auxotrophs (Histidine (50 µg/ml); Cysteine (37 µg/ml); adenine, guanine, thymidine and uracil (7.5 µg/ml); and Vitamins (0.5 µg/ml).

R2YE medium was prepared in the same fashion as R2 medium. However, 5 ml of Difco yeast extract (10%) was added to each 100 ml flask at time of u[illegible].

P (protoplast) buffer was prepared as follows:

A basal solution made up of the following was prepared:

Sucrose (103 grams)

K_2SO_4 (0.25 grams)

$MgCl_2 \bullet 6H_2O$ (2.02 grams)

Trace Element Solution as described for R2 medium (2 ml)

Distilled water to 800 ml

Eighty ml aliquots of the basal solution were then dispensed and autoclaved. Before use, the following was added to each flask in the order listed:

1 ml KH_2PO_4 (0.5%)

10 ml $CaCl_2 \bullet 2H_2O$ (3.68%)

TES buffer (5.75%, adjusted to pH 7.2)

T (transformation) buffer was prepared by mixing the following sterile solutions:

25 ml Sucrose (10.3%)

75 ml distilled water

1 ml Trace Element Solution as described for R2 medium

1 ml K_2SO_4 (2.5%)

The following are then added to 9.3 mls of this solution:

0.2 ml $CaCl_2$ (5M)

0.5 ml Tris maleic acid buffer prepared from 1 M solution of Tris adjusted to pH 8.0 by adding maleic acid.

For use, 3 parts by volume of the above solution are added to 1 part by weight of PEG 1000, previously sterilized by autoclaving.

L (lysis) buffer was prepared by mixing the following sterile solutions:

100 ml Sucrose (10.3%)

10 ml TES buffer (5.73%, adjusted to pH 7.2)

1 ml K_2SO_4 (2.5%)

1 ml Trace Element Solution as described for R2 medium

1 ml KH_2PO_4 (0.5%)

0.1 ml $MgCl_2 \bullet 6H_2O$ (2.5 M)

1 ml $CaCl_2$ (0.25 M)

CRM Medium

A solution containing the following components was prepared in 1 liter of dH_2O: glucose (10 grams), sucrose (103 grams), $MgCl_2 \bullet 6H_2O$ (10.12 grams), BBL™ trypticase soy broth (15 grams) (Becton Dickinson Microbiology Systems, Sparks, Maryland, USA), and BBL™ yeast extract (5 grams) (Becton Dickinson Microbiology Systems). The solution was autoclaved for 30 minutes. Thiostrepton was added to a concentration of 10 µg/ml for cultures propagated with plasmids.

Electroporation Buffer

A solution containing 30% (wt/vol) PEG 1000, 10% glycerol, and 6.5 % sucrose was prepared in dH_2O. The solution was sterilized by vacuum filtration through a 0.22 µm cellulose acetate filter.

Example 2: Extraction of Chromosomal DNA from Strain SC15847

Genomic DNA was isolated from an *Amycolatopsis orientalis* soil isolate strain designation SC15847 (ATCC PT-1043) using a guanidine-detergent lysis method, DNAzol reagent (Invitrogen, Carlsbad, California, USA). The SC15847 culture was grown 24 hours at 28°C in F7 medium (glucose 2.2%, yeast extract 1.0%, malt extract 1.0 %, peptone 0.1%, pH 7.0). Twenty ml of culture was harvested by centrifugation and resuspended in 20 ml of DNAzol, mixed by pipetting and centrifuged 10 minutes in the Beckman TJ6 centrifuge. Ten ml of 100% ethanol was added, inverted several times and stored at room temperature 3 minutes. The DNA was spooled on a glass pipette washed in 100% ethanol and allowed to air dry 10 minutes. The pellet was resuspended in 500 µl of 8mM NaOH and once dissolved it was neutralized with 30 µl of 1M HEPES pH7.2.

Example 3: PCR Reactions

PCR reactions were prepared in a volume of 50 µl, containing 200-500 ng of genomic DNA or 1.0 µl of the cDNA, a forward and reverse primer, and the forward primer being either P450-1$^+$ (SEQ ID NO:23) or P450-1a$^+$(SEQ ID NO:24) or P450-2$^+$(SEQ ID NO:25) and the reverse primer P450-3$^-$ (SEQ ID NO:27)or P450-2$^-$(SEQ ID NO:26). All primers were added to a final concentration of 1.4- 2.0 µM. The PCR

reaction was prepared with 1 µl of Taq enzyme (2.5 units) (Stratagene), 5 µl of Taq buffer and 4 µl of 2.5 mM of dNTPs with dH_2O to 50 µl. The cycling reactions were performed on a Geneamp® PCR system with the following protocol: 95°C for 5 minutes, 5 cycles [95°C 30 seconds, 37°C 15 seconds (30% ramp), 72°C 30 seconds], 35 cycles (94°C 30 seconds, 65°C 15 seconds, 72°C 30 seconds), 72°C 7 minutes. The expected sizes for the reactions are 340 bp for the P450-1^+ (SEQ ID NO:23) or P450-$1a^+$ (SEQ ID NO:24) and P450-3^- (SEQ ID NO:27) primer pairs, 240 bp for the P450-1^+ (SEQ ID NO:23) and P450-2^- (SEQID NO:26) primer pairs and 130 bp for the P450-2^+ (SEQ ID NO:25) and P450-3^- (SEQ ID NO:27) primer pairs.

Example 4: Cloning of Epothilone B Hydroxylase and Ferredoxin Genes

Twenty µg of SC15847 genomic DNA was digested with BglII restriction enzyme for 6 hours at 37°C. A 30k nanosep column (Gelman Sciences, Ann Arbor, Michigan, USA) was used to concentrate the DNA and remove the enzyme and buffer. The reactions were concentrated to 40 µl and washed with 200 µl of TE. The digestion products were then separated a 0.7% agarose gel and genomic DNA in the range of 12~15 kb was excised from the gel and purified using the Qiagen gel extraction method. The genomic DNA was then ligated to plasmid pWB19N (U.S. Patent 5,516,679), which had been digested with BamHI and dephosphorylated using the SAP I enzyme (Roche Molecular Biochemicals, Indianapolis, Indiana, catalog#1 758 250). Ligation reactions were performed in a 15 µl volume with 1U of T4 DNA ligase (Invitrogen) for 1 hour at room temperature. One µl of the ligation was transformed to 100 µl of chemically competent DH10B cells (Invitrogen) and 100 µl plated to five LB agar plates with 30 µg/ml of neomycin, 37°C overnight.

Five nylon membrane circles (Roche Molecular Biochemicals, Indianapolis, Indiana) were numbered and marked for orientation. The membranes were placed on the plates 2 minutes and then allowed to dry for 5 minutes. The membranes were then placed on Whatman filter disks saturated with 10% SDS for 5 minutes, 0.5N NaOH with 1.5 M NaCl for 5 minutes, 1.5 M NaCl with 1.0 M Tris pH 8.0 for 5 minutes, and 15 minutes on 2X SSC. The filters were hybridized as described previously for the Southern hybridization. Hybridizing colonies were picked to 2 ml of TB with 30

μg/ml neomycin and grown overnight at 37°C. Plasmid DNA was isolated using a miniprep column procedure (Mo Bio). This plasmid was named NPB29-1.

Example 5: DNA Sequencing and Analysis

The cloned PCR products were sequenced using fluorescent-dye-labeled terminator cycle sequencing, Big-Dye sequencing kit (Applied Biosystems, Foster city, California, USA) and were analyzed using laser-induced fluorescence capillary electrophoresis, ABI Prism 310 sequencer (Applied Biosystems).

Example 6: Extraction of Total RNA

Total RNA was isolated from the SC15847 culture using a modification of the Chomczynski and Sacchi method with a mono-phasic solution of phenol and guanidine isothiocyanate, Trizol reagent (Invitrogen). Five ml of an SC15847 frozen stock culture was thawed and used to inoculate 100 ml of F7 media in a 500 ml Erlenmeyer flask. The culture was grown in a shaker incubator at 230 rpm, 30°C for 20 hours to an optical density at 600 nm (OD_{600}) of 9.0. The culture was placed in a 16°C shaker incubator at 230 rpm for 20 minutes. Fifty-five milligrams of epothilone B was dissolved in 1 ml of 100% ethanol and added to the culture. A second ml of ethanol was used to rinse the residual epothilone B from the tube and added to the culture. The culture was incubated at 16°C, 230 rpm for 30 hours. Thirty ml of the culture was transferred to a 50 ml tube, 150 mg of lysozyme was added to the culture and the culture was incubated 5 minutes at room temperature. Ten ml of the culture was placed in a 50 ml Falcon tube and centrifuged 5 minutes, 4°C in a TJ6 centrifuge. Two ml of chloroform was added and the tube was mixed vigorously for 15 seconds. The tube was incubated 2 minutes at room temperature and centrifuged 10 minutes, top speed in the TJ6 centrifuge. The aqueous layer was transferred to a fresh tube and 2.5 ml of isopropanol was added to precipitate the RNA. The tube was incubated 10 minutes at room temperature and centrifuged 10 minutes, 4°C. The supernatant was removed, the pellet was rinsed with 70% ethanol and dried briefly under vacuum. The pellet was resuspended in 150 μl of RNase-free dH_2O. Fifty μl of 7.5M LiCl was added to the RNA and incubated at -20°C for 30 minutes. The RNA was pelleted by centrifugation 10 minutes, 4°C in a microcentrifuge. The pellet was rinsed with 200 μl

of 70% ethanol, dried briefly under vacuum and resuspended in 150 µl of RNase free dH_2O.

The RNA was treated with DNaseI (Ambion, Austin, Texas, USA). Twenty-five µl of total RNA (5.3 µg/µl), 2.5 µl of DNaseI buffer, 1.0 µl of DNase I added and incubated at 37°C for 25 minutes. Five µl of DNase I inactivation buffer added, incubated 2 minutes, centrifuged 1 minute, the supernatant was transferred to a fresh tube.

Example 7: cDNA Synthesis

cDNA was synthesized from the total RNA using the Superscript II enzyme (Invitrogen). The reaction was prepared with 1 µl of total RNA (5.3 µg/µl), 9 µl of dH_2O, 1 µl of dNTP mix (10 mM), and 1 µl of random hexamers. The reaction was incubated at 65°C for 5 minutes then placed on ice. The following components were then added: 4 µl of 1st strand buffer, 1 µl of RNase Inhibitor, 2.0 µl of 0.1 M DTT, and 1 µl of Superscript II enzyme. The reaction was incubated at room temperature 10 minutes, 42°C for 50 minutes and 70°C for 15 minutes. One µl of RNaseH was added and incubated 20 minutes at 37°C, 15 minutes at 70°C and stored at 4°C.

Example 8: DNA Labeling

The PCR conditions used to amplify the P450 specific products from genomic DNA and cDNA were used to amplify the insert of plasmid pCRscript-29. Plasmid pCRscript-29 contains a 340bp PCR fragment amplified from SC15847 genomic DNA using primers P450 1^+(SEQ ID NO:23) and P450 3^- (SEQ ID NO:27). Two µl of the plasmid prep was used as a template, with a total of 25 cycles. The amplified product was gel purified using the Qiaquick gel extraction system (Qiagen). The extracted DNA was ethanol precipitated and resuspended in 5 µl of TE, the yield was estimated to be 500 ng. This fragment was labeled with digoxigenin using the chem link labeling reagent (Roche Molecular Biochemicals, Indianapolis, Indiana catalog #1 836 463). Five µl of the PCR product was mixed with 0.5 µl of Dig-chem link and dH_2O added to 20 µl. The reaction was incubated 30 minutes at 85°C and 5 µl of stop solution added. The probe concentration was estimated at 20 ng/µl.

Example 9: Southern DNA Hybridization

Ten µl of genomic DNA (0.5 µg/µl) was digested with BamHI, BglII, EcoRI, HindIII or NotI and separated at 12 volts for 16 hours. The gel was depurinated 10 minutes in 0.25 N HCl and transferred by vacuum to a nylon membrane (Roche Molecular Biochemicals) in 0.4 N NaOH 5" Hg , 90 minutes using a vacuum blotter (Bio-Rad Laboratories, Inc. Hercules, California, USA catalog # 165-5000). The membrane was rinsed in 1 M ammonium acetate and UV-crosslinked using the Stratalinker UV Crosslinker (Stratagene). The membrane was rinsed in 2X SSC and stored at room temperature.

The membrane was prehybridized 1 hour at 42°C in 20 ml of Dig Easy Hyb buffer (Roche Molecular Biochemicals). The probe was denatured 10 minutes at 65°C and then placed on ice. Five ml of probe in Dig-Easy Hyb at an approximate concentration on 20 ng/ml was incubated with the membrane at 42°C overnight. The membrane was washed 2 times in 2X SCC with 0.1% SDS at room temperature, then 2 times in 0.5X SSC with 0.1% SDS at 65°C. The membrane was equilibrated in Genius buffer 1 (10 mM maleic acid, 15 mM NaCl; pH 7.5; 0.3% v/v Tween 20) (Roche Molecular Biochemicals, Indianapolis, Indiana) for 2 minutes, then incubated with 2% blocking solution (2% Blocking reagent in Genius Buffer 1)(Roche Molecular Biochemicals Indianapolis, Indiana) for 1 hour at room temperature. The membrane was incubated with a 1:20,000 dilution of anti-dig antibody in 50 ml of blocking solution for 30 minutes. The membrane was washed 2 times, 15 minutes each in 50 ml of Genius buffer 1. The membrane was equilibrated for two minutes in Genius Buffer 3 (10mM Tris-HCl, 10mM NaCl; pH 9.5). One ml of a 1:100 dilution of CSPD (disodium 3-(4-methoxyspiro{1,2-dioxetane-3,2'-(5'-chloro)tricyclo[3.3.1.1^{3,7}]decan}-4-yl)phenyl phosphate) (Roche Molecular Biochemicals) in Genius buffer 3 was added to the membrane and incubated 5 minutes at room temperature, then placed at 37°C for 15 minutes. The membrane was exposed to Biomax ML film (Kodak, Rochester, New York, USA) for 1 hour.

Example 10: *E. coli* Transformation

Competent cells were purchased from Invitrogen. *E. coli* strain DH10B was used as a host for genomic cloning. The chemically competent cells were thawed on ice and 100 µl aliquoted to a 17 x 100-mm polypropylene tube on ice. One µl of the ligation mixture was added to the cells and incubated on ice for 30 minutes. The cells were incubated at 42°C for 45 seconds, then placed on ice 1-2 minutes. 0.9 ml pf SOC. medium(Invitrogen) was added and the cells were incubated one hour at 30-37°C at 200-240 rpm. Cells were plated on a selective medium (Luria agar with neomycin or ampicillin at a concentration of 30 µg /ml or 100 µg /ml respectively).

Example 11: Transformation of *Streptomyces lividans* TK24

Plasmid pWB19N849 was constructed by digesting plasmid pWB19N with HindIII and treating with SAP I and digesting plasmid pANT849 (Keiser, et al., 2000, Practical Streptomyces Genetics, John Innes) with HindIII. The two linearized fragments were ligated 1 hour at room temperature with 1U of T4 DNA ligase. One µl of the ligation reaction was used to transform XL-1 Blue electrocompetent cells (Stratagene). The recovered cells were plated to LB neomycin (30 µg/ml) overnight at 37°C. Colonies were picked to 2 ml of LB with 30 µg/ml neomycin and incubated overnight at 30°C. MoBio plasmid minipreps were performed on all cultures. Plasmids constructed from the ligation of pWB19N and pANT849 were determined by electrophoretic mobility on 0.7 % agarose. The plasmid pWB19N849 was digested with HindIII and BglII to excise a 5.3 kb fragment equivalent to plasmid pANT849 digested with BglII and HindIII. This 5.3 kb fragment was purified on an agarose gel and extracted using the Qiaquick gel extraction system.

A 1.469 kb DNA fragment containing the epothilone B hydroxylase gene and the downstream ferredoxin gene was amplified using PCR. The 50 µl PCR reaction was composed of 5 µl of Taq buffer, 2.5 µl glycerol, 1 µl of 20 ng/µl NPB29-1 plasmid, 0.4 µl of 25 mM dNTPs, 1.0 µl each of primers NPB29-6F (SEQ ID NO:28) and NPB29-7R (SEQ ID NO:29) (5 pmole/µl), 38.1 µl of dH_2O and 0.5 µl of Taq enzyme (Stratagene). The reactions were performed on a Perkin Elmer 9700, 95°C for 5 minutes, then 30 cycles (96°C for 30 seconds, 60°C 30 seconds, 72°C for 2 minutes), and 72°C for 7 minutes. The PCR product was purified using a Qiagen

minielute column with the PCR cleanup procedure. The purified product was digested with BglII and HindIII and purified on a 0.7 % agarose gel. A 1.469 kb band was excised from the gel and eluted using a Qiagen minielute column. Five µl of this PCR product was ligated with 2 µl of the BglII, HindIII digested pANT849 vector in a 10 µl ligation reaction. The reaction was incubated at room temperature for 24 hours and then transformed to *S. lividans* TK24 protoplasts.

Twenty ml of YEME media was inoculated with a frozen spore suspension of *S. lividans* TK24 and grown 48 hours in a 125 ml bi-indent flask. Protoplasts were prepared as described in Practical Streptomyces Genetics. The ligation reaction was mixed with protoplasts, then 500 µl of transformation buffer was added, followed immediately by 5 ml of P buffer. The transformation reactions were spun down 7 minutes at 2,750 rpm, resuspended in 100 µl of P buffer and plated to one R2YE plate. The plate was incubated at 28°C for 20 hours then overlaid with 5 ml of LB 0.7% agar with 250 µg/ml thiostrepton. After 7 days colonies were picked to an R2YE grid plate with 50 µg/ml of thiostrepton. The colonies were grown an additional 5 days at 28°C, then stored at 4°C.

This recombinant microorganism has been deposited with the ATCC and designated PTA-4022.

Example 12: Transformation of *Streptomyces rimosus*

The procedure of Pigac and Schrempf Appl. Environ Microb., Vol. 61, No. 1, 352-356 (1995) was used to transform *S. rimosus*. *S. rimosus* strain R6 593 was cultivated in 20 ml of CRM medium at 30 °C on a rotary shaker (250 rpm). The cells were harvested at 24 hrs by centrifugation for 5 minutes, 5,000 rpm, 4 °C, and resuspended in 20 ml of 10% sucrose, 4 °C, and centrifuged for 5 minutes, 5,000 rpm, 4 °C. The pellet was resuspended in 10 ml of 15% glycerol, 4 °C and centrifuged for 5 minutes, 5,000 rpm, 4 °C. The pellet was resuspended in 2 ml of 15% glycerol, 4 °C with 100 µg/ml lysozyme and incubated at 37 °C for 30 minutes, centrifuged for 5 minutes, 5,000 rpm, 4 °C and resuspended in 2 ml of 15% glycerol, 4 °C. The 15% glycerol wash was repeated once and the pellet was resuspended in 1 to 2 ml of Electroporation Buffer. The cells were stored at -80°C in 50 – 200 µl aliquots.

The ligations were prepared as described for the *S. lividans* transformation. After the incubation of the ligation reaction, the volume was brought to 100 µl with dH_2O, NaCl was added to 0.3M, and the reaction extracted with an equal volume of 24:1:1 phenol:choroform isoamyl alcohol. Twenty µg of glycogen was added and the ligated DNA was precipitated with 2 volumes of 100% ethanol at –20 °C for 30 minutes. The DNA was pelleted 10 minutes in a microcentrifuge, washed once with 70% ethanol, dried 5 minutes in a speed-vac concentrator and resuspended in 5 µl of dH_2O.

One frozen aliquot of cells was thawed at room temperature and divided, 50 µl/ tube for each DNA sample for electroporation. The cells were stored on ice until use. DNA in 1 to 2 µl of dH_2O was added and mixed. The cell and DNA mixture was transferred to a 2 mm gapped electrocuvette (Bio-Rad Laboratories, Richmond California USA) that was pre-chilled on ice. The cells were electroporated at a setting of 2 kV (10kV/cm), 25µF, 400 Ω using a Gene Pulser™ (Bio-Rad Laboratories). The cells were diluted with 0.75 to 1.0 ml of CRM (0-4 °C), transferred to 15 ml culture tubes and incubated with agitation 3hrs at 30 °C. The cells were plated on trypticase soy broth agar plates with 10-30 µg/ml of thiostrepton.

Example 13: High Performance liquid chromatography

The liquid chromatography separation was performed using a Waters 2690 Separation Module system (Waters Corp., Milford, MA, USA) and a column, 4.6 x

150 mm, filled with SymmetryShield RP_8, particle size 3.5 µm (Waters Corp., Milford, MA, USA). The gradient mobile phase programming was used with a flow rate of 1.0 ml/minute. Eluent A was water/acetonitrile (20:1) + 10 mM ammonium acetate. Eluent B was acetonitrile/water (20:1). The mobile phase was a linear gradient from 12% B to 28 % B over 6 minutes and held isocratic at 28% B over 4 minutes. This was followed by a 28% B to 100% B linear gradient over 20 minutes and a linear gradient to 12% B over two minutes with a 3 minute hold at 12% B.

Example 14: Mass spectrometry

The column effluent was introduced directly into the electrospray ion source of a ZMD mass spectrometer (Micromass, Manchester, UK). The instrument was calibrated using Test Juice reference standard (Waters Corp, Milford, MA, USA) and was delivered at a flow of 10 µl/minute from a syringe pump (Harvard Apparatus, Holliston, MA, USA). The mass spectrometer was operated at a low mass resolution of 13.2 and a high mass resolution of 11.2. Spectra were acquired from using a scan range of *m/z* 100 to 600 at an acquisition rate of 10 spectra /second. The ionization technique employed was positive electrospray (ES). The sprayer voltage was kept at 2900 V and the cone voltage of the ion source was kept at a potential of 17 V.

Example 15: Use of the *ebh* gene sequence (SEQ ID NO:1) to isolate cytochrome P450 genes from other microorganisms

Genomic DNA was isolated from a set of cultures (ATCC43491, ATCC14930, ATCC53630, ATCC53550, ATCC39444, ATCC4333[illegible] ATCC35165) using the DNAzol reagent. The DNA was used as a template for PCR reactions using primers designed to the sequence of the *ebh* gene. Three sets of primers were used for amplification; NPB29-6f (SEQ ID NO:28) and NPB29-7r (SEQ ID NO:29), NPB29-16f (SEQ ID NO:50) and NPB29-17r (SEQ ID NO:51), and NPB29-19f (SEQ ID NO:52) and NPB29-20r (SEQ ID NO:53).

PCR reactions were prepared in a volume of 20 µl, containing 200-500 ng of genomic DNA and a forward and reverse primer. All primers were added to a final concentration of 1.4- 2.0 µM. The PCR reaction was prepared with 0.2 µl of Advantage™ 2 Taq enzyme (BD Biosciences Clontech, Palo Alto, California, USA),

2 µl of Advantage™ 2 Taq buffer and 0.2 µl of 2.5 mM of dNTPs with dH_2O to 20 µl. The cycling reactions were performed on a Geneamp® 9700 PCR system or a Mastercycler® gradient (Eppendorf, Westbury, New York, USA) with the following protocol: 95°C for 5 minutes, 35 cycles (96°C 20 seconds, 54-69°C 30 seconds, 72°C 2 minutes), 72°C for 7 minutes. The expected size of the PCR products is approximately 1469 bp for the NPB29-6f (SEQ ID NO:28) and NPB29-7r (SEQ ID NO:29) primer pair, 1034 bp for the NPB29-16f (SEQ ID NO:50) and NPB29-17r (SEQ ID NO:51) primer pair and 1318 bp for the NPB29-19f (SEQ ID NO:52) and NPB29-20r (SEQ ID NO:53) primer pair. The PCR reactions were analyzed on 0.7% agarose gels. PCR products of the expected size were excised from the gel and purified using the Qiagen gel extraction method. The purified products were sequenced using the Big-Dye sequencing kit and analyzed using an ABI310 sequencer.

Example 16: Construction of plasmid pPCRscript-*ebh*

A 1.469 kb DNA fragment containing the epothilone B hydroxylase gene and the downstream ferredoxin gene was amplified using PCR. The 50 µl PCR reaction was composed of 5 µl of Taq buffer, 2.5 µl glycerol, 1 µl of 20 ng/µl NPB29-1 plasmid, 0.4 µl of 25 mM dNTPs, 1.0 µl each of primers NPB29-6f (SEQ ID NO:28) and NPB29-7r (SEQ ID NO:29) (5 pmole/µl), 38.1 µl of dH_2O and 0.5 µl of Taq enzyme (Stratagene). The reactions were performed on a Geneamp® 9700 PCR system, with the following conditions; 95°C for 5 minutes, then 30 cycles (96°C for 30 seconds, 60°C 30 seconds, 72°C for 2 minutes), and 72°C for 7 minutes. The PCR product was purified using a Qiagen Qiaquick column with the PCR cleanup procedure. The purified product was digested with BglII and HindIII and purified on a 0.7 % agarose gel. A 1.469 kb band was excised from the gel and eluted using a Qiagen Qiaquick gel extraction procedure. The fragments were then cloned into the pPCRscript Amp vector using the PCRscript Amp cloning kit. Colonies containing inserts were picked to 1-2 ml of LB (Luria Broth) with 100 µg/ml ampicillin, 30-37°C, 16-24 hours, 230-300 rpm. Plasmid isolation was performed using the Mo Bio miniplasmid prep kit. The sequence of the insert was confirmed by cycle sequencing with the Big-Dye sequencing kit. This plasmid was named pPCRscript-*ebh*.

Example 17: Mutagenesis of the *ebh* gene for improved yield or altered specificity

The Quikchange® XL Site-Directed Mutagenesis Kit and the Quikchange® Multi Site-Directed Mutagenesis kit, both from Stratagene were used to introduce mutations in the coding region of the *ebh* gene. Both of these methods employ DNA primers 35-45 bases in length containing the desired mutation (SEQ ID NO:54-59 and 71), a methylated circular plasmid template and *PfuTurbo*® DNA Polymerase (U.S. Patent Nos 5,545,552 and 5,866,395 and 5,948,663) to generate copies of the plasmid template incorporating the mutation carried on the mutagenic primers. Subsequent digestion of the reaction with the restriction endonuclease enzyme DpnI, selectively digests the methylated plasmid template, but leaves the non-methylated mutated plasmid intact. The manufacturer's instructions were followed for all procedures with

the exception of the DpnI digestion step in which the incubation time was increased from 1 hr to 3 hrs. The pPCRscript-*ebh* vector was used as the template for mutagenesis.

One to two µl of the reaction was transformed to either XL1-Blue® electrocompetent or XL10-Gold® ultracompetent cells (Stratagene). Cells were plated to a density of greater than 100 colonies per plate on LA (Luria Agar) 100 µg/ml ampicillin plates, and incubated 24-48 hrs at 30-37°C. The entire plate was resuspended in 5 ml of LB containing 100 µg/ml ampicillin. Plasmid was isolated directly from the resuspended cells by centrifuging the cells and then purifying the plasmid using the Mo Bio miniprep procedure. This plasmid was then used as a template for PCR with primers NPB29-6f (SEQ ID NO:28)and NPB29-7r (SEQ ID NO:29) to amplify a mutated expression cassette. Digestion of the 1.469 kb PCR product with the restriction enzymes BglII and HindIII was used to prepare this fragment for ligation to vector pANT849 also digested with BglII and HindIII. Alternatively, the resuspended cells were used to inoculate 20- 50 ml of LB containing 100 µg/ml ampicillin and grown 18-24 hrs at 30-37°C. Qiagen midi-preps were performed on the cultures to isolate plasmid DNA containing the desired mutation. Digestion with the restriction enzymes BglII and HindII was used to excise the mutated expression cassette for ligation to BglII and HindIII digested plasmid pANT849. Screening of mutants was performed in *S. lividans* or *S. rimosus* as described.

Alternatively, the method of Leung *et al.*, Technique-A Journal of Methods in Cell and Molecular Biology, Vol. 1, No. 1, 11-15 (1989) was used to generate random mutation libraries of the *ebh* gene. Manganese and/or reduced dATP concentration is used to control the mutagenesis frequency of the Taq polymerase. The plasmid pCRscript-*ebh* was digested with NotI to linearize the plasmid. The Polymerase buffer was prepared with 0.166 M $(NH_4)_2SO_4$, 0.67M Tris-HCl pH 8.8, 61 mM $MgCl_2$, 67 µM EDTA pH8.0, 1.7 mg/ml Bovine Serum Albumin). The PCR reaction was prepared with 10 µl of Not I digested pCRscript-*ebh* (0.1ng/µl), 10 µl of polymerase buffer, 1.0 µl of 1M β-mercaptoethanol, 10.0 µl of DMSO, 1.0 µl of NPB29-6f (SEQ ID NO:28) primer (100 pmole/µl), 1.0 µl of NPB29-7r (SEQ ID NO:29) primer (100 pmole/µl), 10 µl of 5 mM $MnCl_2$, 10.0 µl 10 mM dGTP, 10.0 µl 2 mM dATP, 10 mM

dTTP, 10.0 µl 10 mM dCTP, and 2.0 µl Taq polymerase. dH_2O was added to 100 µl. Reactions were also prepared as described above but without $MnCl_2$. The cycling reactions were performed a GeneAmp® PCR system with the following protocol: 95°C for 1 minute, 25-30 cycles (94 °C for 1 minute, 55 °C for 30 seconds, 72 °C for 4 minutes), 72 °C for 7 minutes. The PCR reactions were separated on an agarose gel using a Qiagen spin column. The fragments were then digested with BglII and HindIII and purified using a Qiagen spin column. The purified fragments were then ligated to BglII and HindIII digested pANT849 plasmids. Screening of mutants was performed in *S. lividans* and *S. rimosus*.

Table of Characterized Mutants

Mutant	Position	Substitution	Wild-type
*ebh*24-16	92	Valine	Isoleucine
	237	Alanine	Phenylalanine
*ebh*25-1	195	Serine	Asparagine
	294	Proline	Serine
*ebh*10-53	190	Tyrosine	Phenylalanine
	231	Arginine	Glutamic acid
*ebh*24-16d8	92	Valine	Isoleucine
	237	Alanine	Phenylalanine
	67	Glutamine	Arginine
*ebh*24-16c11	92	Valine	Isoleucine
	93	Glycine	Alanine
	237	Alanine	Phenylalanine
	365	Threonine	Isoleucine
*ebh*24-16-16	92	Valine	Isoleucine
	106	Alanine	Valine
	237	Alanine	Phenylalanine
*ebh*24-16-74	88	Histidine	Arginine
	92	Valine	Isoleucine
	237	Alanine	Phenylalanine
ebh-M18	31	Lysine	Glutamic acid
	176	Valine	Methionine
*ebh*24-16g8	92	Valine	Isoleucine

	237	Alanine	Phenylalanine
	67	Glutamine	Arginine
	130	Threonine	Isoleucine
	176	Alanine	Methionine
*ebh*24-16b9	92	Valine	Isoleucine
	237	Alanine	Phenylalanine
	67	Glutamine	Arginine
	140	Threonine	Alanine
	176	Serine	Methionine

Example 18: Comparison of epothilone B transformation in cells expressing *ebh* and mutants thereof

In these experiments, twenty ml of YEME medium in a 125 ml bi-indented flask was inoculated with 200 µl of a frozen spore preparation of *S. lividans* TK24, *S. lividans* (pANT849-*ebh*), *S. lividans* (pANT849-*ebh*10-53) or *S. lividans* (pANT849-*ebh*24-16) and incubated 48 hours at 230 rpm, 30°C. Thiostrepton, 10 µg/ml was added to media inoculated with *S. lividans* (pANT849-*ebh*), *S. lividans* (pANT849-*ebh*10-53) and *S. lividans* (pANT849-*ebh*24-16). Four ml of culture was transferred to 20 ml of R5 medium in a 125 ml Erlenmeyer flask and incubated 18 hrs at 230 rpm, 30°C. Epothilone B in 100% EtOH was added to each culture to a final concentration of 0.05% weight/volume. Samples were taken at 0, 24, 48 and 72 hours with the exception of the *S. lividans* (pANT849-*ebh*24-16) culture, in which the epothilone B had been completely converted to epothilone F at 48 hours. The samples were analyzed by HPLC. Results were calculated as a percentage of the epothilone B at time 0 hours.

Epothilone B:

Time (hours)	TK24	pANT849-*ebh*	pANT849-*ebh*10-53	pANT849-*ebh*24-16
0	100%	100%	100%	100%
24	99%	78%	69%	56%
48	87%	19%	39%	0%
72	87%	0%	3%	---

Epothilone F:

Time (hours)	TK24	pANT849-*ebh*	pANT849-*ebh*10-53	pANT849-*ebh*24-16

0	0%	0%	0%	0%
24	0%	4%	9%	23%
48	0%	21%	29%	52%
72	0%	14%	41%	---

Alternatively, the bioconversion of epothilone B to epothilone F was performed in *S. rimosus* host cells transformed with expression plasmids containing the *ebh* gene and its variants or mutants. One-hundred µl of a frozen *S. rimosus* transformant culture was inoculated to 20 ml CRM media with 10 µg/ml thiostrepton and cultivated 16-24 hr, 30°C, 230- 300 rpm. Epothilone B in 100% ethanol was added to each culture to a final concentration of 0.05% weight/volume. The reaction was typically incubated 20- 40hrs at 30 °C, 230-300 rpm. The concentration of epothilones B and F was determined by HPLC analysis.

Evaluation of mutants in *S. rimosus*

Mutant	Epothilone F yield
ebh-M18	55%
*ebh*24-16d8	75%
*ebh*24-16c11	75%
*ebh*24-16-16	75%
*ebh*24-16-74	75%
*ebh*24-16b9	80%
*ebh*24-16g8	85%

Example 19: Biotransformation of compactin to pravastatin

Twenty ml of R2YE media with 10 µg/ml thiostrepton in a 125 ml flask was inoculated with 200 µl of a frozen spore preparation of *S. lividans* (pANT849), *S. lividans* (pANT849-*ebh*) and incubated 72 hours at 230 rpm, 28°C. Four ml of culture was inoculated to 20 ml of R2YE media and grown 24 hours at 230 rpm, 28°C. One ml of culture was transferred to a 15 ml polypropylene culture tube, 10 µl of compactin (40 mg/ml) was added to each culture and incubated for 24 hours, 28°C, 250 rpm. Five hundred µl of the culture broth was transferred to a fresh 15 ml polypropylene culture tube. Five hundred µl of 50 mM sodium hydroxide was added

and vortexed. Three ml of methanol was added and vortexed, the tube was centrifuged 10 minutes at 3000 rpm in a TJ-6 table-top centrifuge. The organic phase was analyzed by HPLC. Compactin and pravastatin values were assessed relative to the control *S. lividans* (pANT849) culture.

Compactin and Pravastatin as a Percentage of Starting Compactin Concentration:

	S. lividans (pANT849)	*S. lividans* (pANT849-*ebh*)
Compactin	36%	11%
Pravastatin	11%	53%

Example 20: High performance liquid chromatography method for compactin and pravastatin detection

The liquid chromatography separation was performed using a Hewlett Packard1090 Series Separation system (Agilent Technologies, Palo Alto, California, USA) and a column, 50x46 mm, filled with Spherisorb ODS2, particle size 5 µm (Keystone Scientific, Inc, Bellefonte, Pennsylvania, USA). The gradient mobile phase programming was used with a flow rate of 2.0 ml/minute. Eluent A was water, 10 mM ammonium acetate and 0.05% Phosphoric Acid. Eluent B was acetonitrile. The mobile phase was a linear gradient from 20% B to 90 % B over 4 minutes.

Example 21: Structure determination of the biotransformation product of mutant *ebh*25-1

Analytical HPLC was performed using a Hewlett Packard 1100 Series Liquid Chromatograph with a YMC Packed ODS-AQ column, 4.6 mm i.d. x 15 cm l. A gradient system of water (solvent A) and acetonitrile (solvent B) was used: 20% to 90% B linear gradient, 10 minutes; 90% to 20% linear gradient, 2 minutes. The flow rate was 1 ml/minute and UV detection was at 254 nm.

Preparative HPLC was performed using the following equipment and conditions:

Pump: Varian ProStar Solvent Delivery Module (Varian Inc., Palo Alto, California, USA). Detector: Gynkotek UVD340S.

Column: YMC ODS-A column (30mmID X 100 mm length, 5µ particle size).

Elution flow rate: 30 ml/minute

Elution gradient: (solvent A: water; solvent B: acetonitrile), 20% B, 2 minutes; 20% to 60% B linear gradient, 18 minutes; 60% B, 2 minutes; 60 % to 90% B linear gradient, 1 minute; 90 % B, 3 minutes; 90 % to 20% B linear gradient, 2 minutes.

Detection: UV, 210 nm.

LC/NMR was performed as follows: 40 µl of sample was injected onto a YMC Packed ODS-AQ column (4.6 mm i.d. x 15 cm l). The column was eluted at 1 ml/minute flow rate with a gradient system of D_2O (solvent A) and acetonitrile-d_3 (solvent B): 30% B, 1 minute; 30% to 80% B linear gradient, 11 minutes. The eluent passed a UV detection cell (monitored at 254 nm) before flowing through a F19/H1 NMR probe (60 µl active volume) in Varian AS-600 NMR spectrometer. The biotransformation product was eluted at around 7.5 minutes and the flow was stopped manually to allow the eluent to remain in the NMR probe for NMR data acquisition.

Isolation and analysis was performed as follows. The butanol/methanol extract (about 10 ml) was evaporated to dryness under nitrogen stream. One ml methanol was added to the residue (38 mg) and insoluble material was removed by centrifugation (13000 rpm, 2 min). 0.1 ml of the supernatant was used for LC/NMR study and the rest of 0.9 ml was subjected to the preparative HPLC (0.2-0.4 ml per injection). Two major peaks were observed and collected: peak A was eluted between 14 and 15 minutes, while peak B was eluted between 16.5 and 17.5 minutes. Analytical HPLC analysis indicated that peak B was the parent compound, epothilone B (Rt 8.5 minutes), and peak A was the biotransformation product (Rt 7.3 minutes). The peak A fractions were pooled and MS analysis data was obtained with the pooled fractions. The pooled fraction was evaporated to a small volume, then was lyophilized to give 3 mg of white solid. NMR and HPLC analysis of the white solid (dissolved in methanol) revealed that the biotransformation product was partially decomposed during the drying process.

APPENDIX 1

Atom No.	Residue	Atom Name	X-coord	Y-coord	Z-coord
1	ALA9	N	-39.918	-4.913	-1.651
2	ALA9	CA	-38.454	-5.033	-1.537
3	ALA9	C	-37.953	-4.886	-0.099
4	ALA9	O	-38.625	-4.31	0.765
5	ALA9	CB	-37.809	-3.967	-2.415
6	THR10	N	-36.781	-5.447	0.146
7	THR10	CA	-36.187	-5.437	1.49
8	THR10	C	-34.916	-4.585	1.553
9	THR10	O	-34.016	-4.735	0.72
10	THR10	CB	-35.871	-6.887	1.846
11	THR10	OG1	-37.075	-7.631	1.717
12	THR10	CG2	-35.355	-7.053	3.271
13	LEU11	N	-34.858	-3.699	2.536
14	LEU11	CA	-33.669	-2.853	2.745
15	LEU11	C	-32.511	-3.649	3.353
16	LEU11	O	-32.706	-4.468	4.259
17	LEU11	CB	-34.033	-1.707	3.687
18	LEU11	CG	-35.079	-0.78	3.078
19	LEU11	CD1	-35.53	0.265	4.091
20	LEU11	CD2	-34.555	-0.111	1.81
21	PRO12	N	-31.32	-3.422	2.823
22	PRO12	CA	-30.121	-4.119	3.302
23	PRO12	C	-29.652	-3.606	4.663
24	PRO12	O	-29.656	-2.397	4.918
25	PRO12	CB	-29.081	-3.842	2.259
26	PRO12	CG	-29.597	-2.771	1.309
27	PRO12	CD	-31.031	-2.493	1.729
28	LEU13	N	-29.278	-4.522	5.54
29	LEU13	CA	-28.676	-4.118	6.819
30	LEU13	C	-27.183	-3.88	6.627
31	LEU13	O	-26.449	-4.806	6.267
32	LEU13	CB	-28.898	-5.196	7.872
33	LEU13	CG	-30.374	-5.354	8.217
34	LEU13	CD1	-30.587	-6.516	9.181
35	LEU13	CD2	-30.945	-4.067	8.802
36	ALA14	N	-26.72	-2.741	7.112
37	ALA14	CA	-25.355	-2.266	6.825
38	ALA14	C	-24.244	-2.941	7.634
39	ALA14	O	-23.058	-2.719	7.372
40	ALA14	CB	-25.311	-0.764	7.075
41	ARG15	N	-24.628	-3.792	8.569
42	ARG15	CA	-23.664	-4.537	9.379
43	ARG15	C	-23.478	-5.983	8.91
44	ARG15	O	-22.815	-6.767	9.599
45	ARG15	CB	-24.174	-4.519	10.81
46	ARG15	CG	-25.655	-4.879	10.84
47	ARG15	CD	-26.2	-4.843	12.26
48	ARG15	NE	-27.657	-5.039	12.256
49	ARG15	CZ	-28.358	-5.301	13.36
50	ARG15	NH1	-29.69	-5.376	13.3
51	ARG15	NH2	-27.735	-5.412	14.536
52	LYS16	N	-24.096	-6.351	7.798

53	LYS16	CA	-24.016	-7.741	7.335
54	LYS16	C	-22.639	-8.128	6.807
55	LYS16	O	-21.959	-7.359	6.115
56	LYS16	CB	-25.061	-7.977	6.252
57	LYS16	CG	-26.466	-7.985	6.839
58	LYS16	CD	-26.605	-9.079	7.892
59	LYS16	CE	-28.002	-9.092	8.499
60	LYS16	NZ	-28.113	-10.128	9.537
61	CYS17	N	-22.317	-9.392	7.036
62	CYS17	CA	-21.061	-10.004	6.56
63	CYS17	C	-20.737	-9.771	5.066
64	CYS17	O	-19.662	-9.205	4.833
65	CYS17	CB	-21.096	-11.501	6.864
66	CYS17	SG	-21.33	-11.937	8.602
67	PRO18	N	-21.635	-10.003	4.1
68	PRO18	CA	-21.293	-9.756	2.683
69	PRO18	C	-21.123	-8.291	2.246
70	PRO18	O	-21.013	-8.061	1.036
71	PRO18	CB	-22.388	-10.383	1.878
72	PRO18	CG	-23.509	-10.812	2.802
73	PRO18	CD	-23.002	-10.554	4.207
74	PHE19	N	-21.137	-7.33	3.162
75	PHE19	CA	-20.792	-5.947	2.834
76	PHE19	C	-19.279	-5.777	2.788
77	PHE19	O	-18.789	-4.92	2.036
78	PHE19	CB	-21.36	-5.007	3.894
79	PHE19	CG	-22.8	-4.568	3.654
80	PHE19	CD1	-23.051	-3.27	3.232
81	PHE19	CD2	-23.856	-5.444	3.867
82	PHE19	CE1	-24.355	-2.853	3.003
83	PHE19	CE2	-25.159	-5.03	3.629
84	PHE19	CZ	-25.409	-3.735	3.197
85	SER20	N	-18.573	-6.687	3.449
86	SER20	CA	-17.102	-6.717	3.446
87	SER20	C	-16.569	-7.839	4.342
88	SER20	O	-16.632	-7.723	5.573
89	SER20	CB	-16.557	-5.371	3.929
90	SER20	OG	-17.236	-5.019	5.129
91	PRO21	N	-15.974	-8.867	3.753
92	PRO21	CA	-15.978	-9.134	2.304
93	PRO21	C	-17.267	-9.836	1.856
94	PRO21	O	-18.026	-10.327	2.702
95	PRO21	CB	-14.8	-10.047	2.111
96	PRO21	CG	-14.442	-10.669	3.455
97	PRO21	CD	-15.306	-9.949	4.481
98	PRO22	N	-17.551	-9.859	0.561
99	PRO22	CA	-16.897	-9.007	-0.445
100	PRO22	C	-17.4	-7.575	-0.[illegible]3
101	PRO22	O	-18.341	-7.371	0.469
102	PRO22	CB	-17.32	-9.591	-1.762
103	PRO22	CG	-18.478	-10.549	-1.528
104	PRO22	CD	-18.669	-10.604	-0.021
105	PRO23	N	-16.687	-6.605	-0.842
106	PRO23	CA	-17.224	-5.241	-0.897

107	PRO23	C	-18.525	-5.21	-1.693
108	PRO23	O	-18.524	-5.083	-2.925
109	PRO23	CB	-16.159	-4.417	-1.547
110	PRO23	CG	-15.004	-5.321	-1.95
111	PRO23	CD	-15.388	-6.725	-1.509
112	GLU24	N	-19.62	-5.122	-0.956
113	GLU24	CA	-20.963	-5.192	-1.547
114	GLU24	C	-21.415	-3.843	-2.088
115	GLU24	O	-22.323	-3.794	-2.93
116	GLU24	CB	-21.934	-5.68	-0.48
117	GLU24	CG	-23.27	-6.137	-1.052
118	GLU24	CD	-23.982	-7.017	-0.024
119	GLU24	OE1	-24.613	-7.981	-0.433
120	GLU24	OE2	-23.833	-6.745	1.158
121	TYR25	N	-20.573	-2.843	-1.878
122	TYR25	CA	-20.842	-1.47	-2.303
123	TYR25	C	-20.704	-1.311	-3.816
124	TYR25	O	-21.364	-0.436	-4.385
125	TYR25	CB	-19.828	-0.568	-1.608
126	TYR25	CG	-19.616	-0.882	-0.128
127	TYR25	CD1	-20.662	-0.753	0.779
128	TYR25	CD2	-18.364	-1.298	0.311
129	TYR25	CE1	-20.461	-1.062	2.119
130	TYR25	CE2	-18.163	-1.605	1.65
131	TYR25	CZ	-19.213	-1.492	2.55
132	TYR25	OH	-19.026	-1.859	3.866
133	GLU26	N	-20.1	-2.296	-4.468
134	GLU26	CA	-20.009	-2.293	-5.928
135	GLU26	C	-21.404	-2.483	-6.52
136	GLU26	O	-21.92	-1.572	-7.177
137	GLU26	CB	-19.129	-3.454	-6.39
138	GLU26	CG	-17.813	-3.593	-5.628
139	GLU26	CD	-16.94	-2.342	-5.707
140	GLU26	OE1	-16.345	-2.12	-6.749
141	GLU26	OE2	-16.773	-1.731	-4.657
142	ARG27	N	-22.105	-3.488	-6.017
143	ARG27	CA	-23.437	-3.805	-6.538
144	ARG27	C	-24.504	-2.909	-5.921
145	ARG27	O	-25.496	-2.591	-6.59
146	ARG27	CB	-23.752	-5.26	-6.22
147	ARG27	CG	-22.7	-6.189	-6.812
148	ARG27	CD	-23.031	-7.653	-6.55
149	ARG27	NE	-23.146	-7.926	-5.108
150	ARG27	CZ	-22.251	-8.648	-4.428
151	ARG27	NH1	-21.16	-9.11	-5.043
152	ARG27	NH2	-22.428	-8.879	-3.126
153	LEU28	N	-24.197	-2.331	-4.771
154	LEU28	CA	-25.11	-1.358	-4.168
155	LEU28	C	-25.131	-0.079	-4.987
156	LEU28	O	-26.214	0.286	-5.45
157	LEU28	CB	-24.67	-1.039	-2.746
158	LEU28	CG	-24.868	-2.224	-1.81
159	LEU28	CD1	-24.303	-1.916	-0.43
160	LEU28	CD2	-26.34	-2.609	-1.716

161	ARG29	N	-23.969	0.307	-5.49
162	ARG29	CA	-23.835	1.502	-6.327
163	ARG29	C	-24.521	1.334	-7.677
164	ARG29	O	-25.271	2.226	-8.096
165	ARG29	CB	-22.345	1.682	-6.568
166	ARG29	CG	-21.997	2.947	-7.336
167	ARG29	CD	-20.519	2.941	-7.711
168	ARG29	NE	-19.696	2.563	-6.551
169	ARG29	CZ	-18.945	1.459	-6.523
170	ARG29	NH1	-18.872	0.673	-7.6
171	ARG29	NH2	-18.265	1.145	-5.421
172	ARG30	N	-24.494	0.109	-8.182
173	ARG30	CA	-25.112	-0.208	-9.475
174	ARG30	C	-26.629	-0.386	-9.407
175	ARG30	O	-27.282	-0.429	-10.455
176	ARG30	CB	-24.503	-1.512	-9.971
177	ARG30	CG	-22.992	-1.401	-10.1
178	ARG30	CD	-22.376	-2.745	-10.463
179	ARG30	NE	-20.909	-2.659	-10.479
180	ARG30	CZ	-20.12	-3.648	-10.054
181	ARG30	NH1	-20.658	-4.772	-9.576
182	ARG30	NH2	-18.793	-3.508	-10.099
183	GLU31	N	-27.194	-0.493	-8.215
184	GLU31	CA	-28.653	-0.576	-8.109
185	GLU31	C	-29.207	0.713	-7.51
186	GLU31	O	-30.393	1.032	-7.656
187	GLU31	CB	-29.025	-1.746	-7.203
188	GLU31	CG	-28.381	-3.055	-7.65
189	GLU31	CD	-28.814	-3.443	-9.061
190	GLU31	OE1	-30.013	-3.448	-9.301
191	GLU31	OE2	-27.961	-3.944	-9.782
192	SER32	N	-28.319	1.439	-6.855
193	SER32	CA	-28.652	2.672	-6.147
194	SER32	C	-27.386	3.393	-5.683
195	SER32	O	-26.706	2.984	-4.731
196	SER32	CB	-29.509	2.309	-4.939
197	SER32	OG	-28.842	1.268	-4.234
198	PRO33	N	-27.148	4.543	-6.292
199	PRO33	CA	-26.039	5.408	-5.869
200	PRO33	C	-26.227	5.972	-4.454
201	PRO33	O	-25.241	6.254	-3.758
202	PRO33	CB	-26.023	6.511	-6.879
203	PRO33	CG	-27.203	6.364	-7.829
204	PRO33	CD	-27.933	5.107	-7.394
205	VAL34	N	-27.478	6.094	-4.033
206	VAL34	CA	-27.83	6.472	-2.661
207	VAL34	C	-28.828	5.447	-2.122
208	VAL34	O	-30.01	5.467	-2.487
209	VAL34	CB	-28.483	7.85	-2.686
210	VAL34	CG1	-28.789	8.339	-1.275
211	VAL34	CG2	-27.616	8.865	-3.42
212	SER35	N	-28.344	4.546	-1.286
213	SER35	CA	-29.186	3.438	-0.802
214	SER35	C	-29.512	3.536	0.688

215	SER35	O	-28.615	3.692	1.521
216	SER35	CB	-28.456	2.126	-1.077
217	SER35	OG	-27.19	2.169	-0.43
218	ARG36	N	-30.785	3.413	1.025
219	ARG36	CA	-31.168	3.431	2.443
220	ARG36	C	-30.894	2.072	3.082
221	ARG36	O	-31.516	1.059	2.741
222	ARG36	CB	-32.645	3.779	2.597
223	ARG36	CG	-33.016	3.857	4.076
224	ARG36	CD	-34.513	4.047	4.295
225	ARG36	NE	-34.987	5.35	3.804
226	ARG36	CZ	-36.272	5.582	3.523
227	ARG36	NH1	-37.16	4.59	3.609
228	ARG36	NH2	-36.662	6.791	3.113
229	VAL37	N	-29.921	2.067	3.974
230	VAL37	CA	-29.543	0.855	4.695
231	VAL37	C	-29.982	0.926	6.152
232	VAL37	O	-30.313	1.995	6.684
233	VAL37	CB	-28.03	0.681	4.608
234	VAL37	CG1	-27.591	0.391	3.177
235	VAL37	CG2	-27.298	1.898	5.163
236	GLY38	N	-30.064	-0.24	6.761
237	GLY38	CA	-30.404	-0.332	8.18
238	GLY38	C	-29.151	-0.563	9.016
239	GLY38	O	-28.562	-1.652	9.003
240	LEU39	N	-28.764	0.463	9.75
241	LEU39	CA	-27.607	0.399	10.656
242	LEU39	C	-27.911	-0.554	11.817
243	LEU39	O	-29.028	-1.085	11.882
244	LEU39	CB	-27.353	1.814	11.187
245	LEU39	CG	-26.198	2.546	10.5
246	LEU39	CD1	-26.368	2.665	8.988
247	LEU39	CD2	-26.011	3.925	11.12
248	PRO40	N	-26.919	-0.869	12.643
249	PRO40	CA	-27.183	-1.62	13.875
250	PRO40	C	-28.423	-1.116	14.614
251	PRO40	O	-28.771	0.073	14.574
252	PRO40	CB	-25.933	-1.51	14.691
253	PRO40	CG	-24.84	-0.886	13.837
254	PRO40	CD	-25.497	-0.52	12.516
255	SER41	N	-29.188	-2.109	15.042
256	SER41	CA	-30.511	-1.986	15.686
257	SER41	C	-31.548	-1.213	14.856
258	SER41	O	-32.379	-0.492	15.419
259	SER41	CB	-30.387	-1.382	17.087
260	SER41	OG	-30.036	-0.008	17.001
261	GLY42	N	-31.474	-1.34	13.539
262	GLY42	CA	-32.521	-0.831	12.644
263	GLY42	C	-32.557	0.686	12.434
264	GLY42	O	-33.59	1.208	11.997
265	GLN43	N	-31.471	1.392	12.713
266	GLN43	CA	-31.501	2.847	12.494
267	GLN43	C	-31.201	3.16	11.025
268	GLN43	O	-30.079	2.955	10.551

269	GLN43	CB	-30.507	3.53	13.437
270	GLN43	CG	-30.681	5.05	13.439
271	GLN43	CD	-29.873	5.699	14.567
272	GLN43	OE1	-30.31	6.682	15.184
273	GLN43	NE2	-28.723	5.116	14.852
274	THR44	N	-32.227	3.582	10.304
275	THR44	CA	-32.096	3.832	8.859
276	THR44	C	-31.194	5.02	8.534
277	THR44	O	-31.231	6.071	9.187
278	THR44	CB	-33.475	4.077	8.258
279	THR44	OG1	-34.009	5.268	8.823
280	THR44	CG2	-34.428	2.923	8.551
281	ALA45	N	-30.35	4.799	7.541
282	ALA45	CA	-29.426	5.833	7.07
283	ALA45	C	-29.16	5.718	5.572
284	ALA45	O	-29.105	4.619	5.009
285	ALA45	CB	-28.115	5.705	7.836
286	TRP46	N	-28.989	6.859	4.931
287	TRP46	CA	-28.702	6.865	3.492
288	TRP46	C	-27.212	6.698	3.221
289	TRP46	O	-26.408	7.589	3.517
290	TRP46	CB	-29.185	8.173	2.881
291	TRP46	CG	-30.693	8.309	2.805
292	TRP46	CD1	-31.509	9.009	3.665
293	TRP46	CD2	-31.552	7.723	1.804
294	TRP46	NE1	-32.788	8.894	3.228
295	TRP46	CE2	-32.862	8.146	2.116
296	TRP46	CE3	-31.324	6.922	0.701
297	TRP46	CZ2	-33.913	7.774	1.295
298	TRP46	CZ3	-32.389	6.538	-0.105
299	TRP46	CH2	-33.68	6.967	0.19
300	ALA47	N	-26.863	5.559	2.652
301	ALA47	CA	-25.475	5.257	2.302
302	ALA47	C	-25.153	5.708	0.882
303	ALA47	O	-25.772	5.272	-0.1
304	ALA47	CB	-25.248	3.756	2.427
305	LEU48	N	-24.185	6.602	0.797
306	LEU48	CA	-23.751	7.129	-0.501
307	LEU48	C	-22.648	6.252	-1.067
308	LEU48	O	-21.546	6.197	-0.511
309	LEU48	CB	-23.222	8.543	-0.317
310	LEU48	CG	-24.27	9.464	0.289
311	LEU48	CD1	-23.707	10.863	0.454
312	LEU48	CD2	-25.524	9.515	-0.569
313	THR49	N	-22.948	5.601	-2.176
314	THR49	CA	-22.01	4.636	-2.75
315	THR49	C	-21.197	5.214	-3.907
316	THR49	O	-20.047	4.803	-4.09
317	THR49	CB	-22.774	3.391	-3.196
318	THR49	OG1	-23.783	3.769	-4.125
319	THR49	CG2	-23.458	2.703	-2.02
320	ARG50	N	-21.724	6.2	-4.616
321	ARG50	CA	-20.899	6.838	-5.655
322	ARG50	C	-20.007	7.927	-5.081

323	ARG50	O	-20.456	8.712	-4.234
324	ARG50	CB	-21.737	7.467	-6.758
325	ARG50	CG	-22.426	6.441	-7.639
326	ARG50	CD	-22.852	7.085	-8.951
327	ARG50	NE	-23.597	8.327	-8.704
328	ARG50	CZ	-23.779	9.27	-9.629
329	ARG50	NH1	-24.462	10.375	-9.326
330	ARG50	NH2	-23.274	9.111	-10.854
331	LEU51	N	-18.92	8.175	-5.797
332	LEU51	CA	-17.931	9.19	-5.399
333	LEU51	C	-18.52	10.584	-5.583
334	LEU51	O	-18.42	11.426	-4.682
335	LEU51	CB	-16.726	9.066	-6.33
336	LEU51	CG	-15.377	9.193	-5.621
337	LEU51	CD1	-14.233	9.154	-6.628
338	LEU51	CD2	-15.267	10.433	-4.746
339	GLU52	N	-19.404	10.68	-6.562
340	GLU52	CA	-20.088	11.93	-6.891
341	GLU52	C	-21.101	12.314	-5.811
342	GLU52	O	-21.114	13.477	-5.389
343	GLU52	CB	-20.821	11.759	-8.229
344	GLU52	CG	-19.897	11.56	-9.439
345	GLU52	CD	-19.749	10.09	-9.853
346	GLU52	OE1	-19.796	9.24	-8.971
347	GLU52	OE2	-19.502	9.849	-11.025
348	ASP53	N	-21.659	11.313	-5.146
349	ASP53	CA	-22.646	11.572	-4.096
350	ASP53	C	-21.953	11.905	-2.783
351	ASP53	O	-22.4	12.804	-2.063
352	ASP53	CB	-23.493	10.322	-3.876
353	ASP53	CG	-24.263	9.94	-5.133
354	ASP53	OD1	-24.319	8.749	-5.405
355	ASP53	OD2	-24.633	10.838	-5.878
356	ILE54	N	-20.75	11.382	-2.614
357	ILE54	CA	-19.991	11.62	-1.387
358	ILE54	C	-19.301	12.976	-1.41
359	ILE54	O	-19.36	13.7	-0.409
360	ILE54	CB	-18.963	10.509	-1.269
361	ILE54	CG1	-19.674	9.167	-1.252
362	ILE54	CG2	-18.113	10.671	-0.015
363	ILE54	CD1	-18.677	8.03	-1.365
364	ARG55	N	-18.916	13.43	-2.592
365	ARG55	CA	-18.346	14.776	-2.704
366	ARG55	C	-19.44	15.836	-2.679
367	ARG55	O	-19.252	16.893	-2.065
368	ARG55	CB	-17.551	14.883	-3.998
369	ARG55	CG	-16.293	14.028	-3.94
370	ARG55	CD	-15.498	14.133	-5.235
371	ARG55	NE	-16.277	13.61	-6.367
372	ARG55	CZ	-15.712	13.028	-7.427
373	ARG55	NH1	-14.383	12.947	-7.513
374	ARG55	NH2	-16.475	12.553	-8.413
375	GLU56	N	-20.64	15.438	-3.068
376	GLU56	CA	-21.795	16.331	-2.984

377	GLU56	C	-22.287	16.444	-1.539
378	GLU56	O	-22.628	17.546	-1.095
379	GLU56	CB	-22.875	15.722	-3.866
380	GLU56	CG	-24.103	16.605	-4.028
381	GLU56	CD	-25.112	15.838	-4.874
382	GLU56	OE1	-25.906	16.463	-5.56
383	GLU56	OE2	-25.055	14.616	-4.834
384	MET57	N	-22.065	15.392	-0.767
385	MET57	CA	-22.379	15.386	0.665
386	MET57	C	-21.4	16.241	1.459
387	MET57	O	-21.827	17.091	2.248
388	MET57	CB	-22.242	13.948	1.141
389	MET57	CG	-22.423	13.805	2.646
390	MET57	SD	-21.979	12.184	3.306
391	MET57	CE	-20.221	12.196	2.89
392	LEU58	N	-20.14	16.197	1.056
393	LEU58	CA	-19.089	16.973	1.726
394	LEU58	C	-19.07	18.444	1.307
395	LEU58	O	-18.398	19.263	1.946
396	LEU58	CB	-17.751	16.327	1.389
397	LEU58	CG	-17.638	14.941	2.013
398	LEU58	CD1	-16.504	14.133	1.394
399	LEU58	CD2	-17.49	15.03	3.528
400	SER59	N	-19.807	18.776	0.261
401	SER59	CA	-19.959	20.171	-0.144
402	SER59	C	-21.305	20.739	0.304
403	SER59	O	-21.531	21.951	0.204
404	SER59	CB	-19.852	20.24	-1.661
405	SER59	OG	-18.59	19.697	-2.022
406	SER60	N	-22.175	19.879	0.807
407	SER60	CA	-23.5	20.318	1.246
408	SER60	C	-23.505	20.806	2.685
409	SER60	O	-23.464	19.996	3.62
410	SER60	CB	-24.477	19.156	1.138
411	SER60	OG	-25.689	19.581	1.749
412	PRO61	N	-23.91	22.058	2.835
413	PRO61	CA	-24.023	22.695	4.154
414	PRO61	C	-25.231	22.233	4.983
415	PRO61	O	-25.41	22.7	6.113
416	PRO61	CB	-24.145	24.157	3.853
417	PRO61	CG	-24.401	24.343	2.364
418	PRO61	CD	-24.301	22.959	1.747
419	HIS62	N	-26.044	21.333	4.451
420	HIS62	CA	-27.21	20.856	5.18
421	HIS62	C	-26.949	19.497	5.813
422	HIS62	O	-27.863	18.935	6.427
423	HIS62	CB	-28.379	20.764	4.214
424	HIS62	CG	-28.703	22.084	3.55
425	HIS62	ND1	-28.955	23.252	4.171
426	HIS62	CD2	-28.796	22.32	2.198
427	HIS62	CE1	-29.197	24.205	3.248
428	HIS62	NE2	-29.098	23.627	2.029
429	PHE63	N	-25.765	18.945	5.596
430	PHE63	CA	-25.385	17.693	6.258

431	PHE63	C	-24.492	17.977	7.456
432	PHE63	O	-23.261	17.885	7.396
433	PHE63	CB	-24.686	16.783	5.262
434	PHE63	CG	-25.651	16.13	4.284
435	PHE63	CD1	-26.92	15.76	4.71
436	PHE63	CD2	-25.265	15.901	2.972
437	PHE63	CE1	-27.804	15.161	3.824
438	PHE63	CE2	-26.147	15.298	2.087
439	PHE63	CZ	-27.415	14.928	2.512
440	SER64	N	-25.159	18.211	8.569
441	SER64	CA	-24.502	18.656	9.795
442	SER64	C	-23.765	17.525	10.507
443	SER64	O	-24.07	16.34	10.339
444	SER64	CB	-25.587	19.225	10.7
445	SER64	OG	-24.96	19.785	11.84
446	SER65	N	-22.719	17.898	11.218
447	SER65	CA	-22.006	16.938	12.053
448	SER65	C	-22.463	17.032	13.513
449	SER65	O	-22.031	16.247	14.365
450	SER65	CB	-20.522	17.234	11.936
451	SER65	OG	-20.167	17.174	10.564
452	ASP66	N	-23.368	17.961	13.782
453	ASP66	CA	-23.901	18.186	15.122
454	ASP66	C	-25.388	18.496	14.919
455	ASP66	O	-25.978	18.026	13.938
456	ASP66	CB	-23.149	19.393	15.69
457	ASP66	CG	-22.904	19.311	17.192
458	ASP66	OD1	-21.835	19.724	17.618
459	ASP66	OD2	-23.871	19.048	17.899
460	ARG67	N	-25.972	19.246	15.842
461	ARG67	CA	-27.32	19.831	15.692
462	ARG67	C	-28.423	18.78	15.619
463	ARG67	O	-28.768	18.296	14.533
464	ARG67	CB	-27.384	20.684	14.423
465	ARG67	CG	-26.263	21.716	14.336
466	ARG67	CD	-26.329	22.778	15.428
467	ARG67	NE	-25.137	23.64	15.358
468	ARG67	CZ	-25.091	24.799	14.695
469	ARG67	NH1	-26.189	25.28	14.107
470	ARG67	NH2	-23.957	25.503	14.663
471	GLN68	N	-28.983	18.45	16.768
472	GLN68	CA	-30.127	17.538	16.79
473	GLN68	C	-31.414	18.348	16.65
474	GLN68	O	-31.728	19.187	17.503
475	GLN68	CB	-30.116	16.757	18.1
476	GLN68	CG	-31.207	15.692	18.12
477	GLN68	CD	-31.109	14.852	19.389
478	GLN68	OE1	-31.941	14.973	20.296
479	GLN68	NE2	-30.137	13.955	19.406
480	SER69	N	-32.129	18.102	15.565
481	SER69	CA	-33.37	18.833	15.272
482	SER69	C	-34.444	18.558	16.32
483	SER69	O	-34.447	17.495	16.958
484	SER69	CB	-33.885	18.387	13.91

485	SER69	OG	-34.261	17.025	14.033
486	PRO70	N	-35.332	19.526	16.499
487	PRO70	CA	-36.438	19.385	17.447
488	PRO70	C	-37.244	18.122	17.171
489	PRO70	O	-37.547	17.795	16.018
490	PRO70	CB	-37.267	20.622	17.291
491	PRO70	CG	-36.6	21.547	16.285
492	PRO70	CD	-35.348	20.824	15.815
493	SER71	N	-37.424	17.369	18.245
494	SER71	CA	-38.115	16.065	18.289
495	SER71	C	-37.589	15.02	17.298
496	SER71	O	-38.378	14.228	16.769
497	SER71	CB	-39.625	16.244	18.111
498	SER71	OG	-39.919	16.638	16.777
499	PHE72	N	-36.282	14.985	17.081
500	PHE72	CA	-35.679	13.876	16.321
501	PHE72	C	-34.364	13.43	16.957
502	PHE72	O	-33.281	13.768	16.458
503	PHE72	CB	-35.428	14.283	14.872
504	PHE72	CG	-36.682	14.456	14.018
505	PHE72	CD1	-37.097	15.724	13.63
506	PHE72	CD2	-37.402	13.339	13.617
507	PHE72	CE1	-38.238	15.875	12.853
508	PHE72	CE2	-38.544	13.489	12.84
509	PHE72	CZ	-38.962	14.758	12.459
510	PRO73	N	-34.469	12.59	17.979
511	PRO73	CA	-33.31	12.19	18.786
512	PRO73	C	-32.522	11.027	18.18
513	PRO73	O	-32.606	9.895	18.668
514	PRO73	CB	-33.898	11.776	20.099
515	PRO73	CG	-35.392	11.555	19.917
516	PRO73	CD	-35.708	12.004	18.5
517	LEU74	N	-31.772	11.304	17.127
518	LEU74	CA	-30.933	10.263	16.521
519	LEU74	C	-29.707	9.976	17.375
520	LEU74	O	-29.08	10.892	17.926
521	LEU74	CB	-30.474	10.697	15.135
522	LEU74	CG	-31.627	10.794	14.146
523	LEU74	CD1	-31.094	11.194	12.776
524	LEU74	CD2	-32.381	9.471	14.05
525	MET75	N	-29.359	8.705	17.454
526	MET75	CA	-28.167	8.306	18.208
527	MET75	C	-27.099	7.808	17.243
528	MET75	O	-27.166	6.675	16.746
529	MET75	CB	-28.539	7.208	19.198
530	MET75	CG	-27.367	6.867	20.114
531	MET75	SD	-27.6	5.549	21.31
532	MET75	CE	-28.0	4.197	20.154
533	VAL76	N	-26.1	8.657	16.992
534	VAL76	CA	-25.07	8.327	16.017
535	VAL76	C	-24.274	7.103	16.455
536	VAL76	O	-23.953	6.925	17.636
537	VAL76	CB	-24.151	9.527	15.809
538	VAL76	CG1	-24.904	10.676	15.149

539	VAL76	CG2	-23.504	9.986	17.109
540	ALA77	N	-23.836	6.34	15.467
541	ALA77	CA	-23.158	5.062	15.727
542	ALA77	C	-21.703	5.203	16.177
543	ALA77	O	-21.033	4.194	16.42
544	ALA77	CB	-23.22	4.212	14.465
545	ARG78	N	-21.218	6.431	16.271
546	ARG78	CA	-19.868	6.689	16.762
547	ARG78	C	-19.868	7.178	18.215
548	ARG78	O	-18.816	7.163	18.865
549	ARG78	CB	-19.274	7.772	15.874
550	ARG78	CG	-19.445	7.436	14.398
551	ARG78	CD	-19.068	8.629	13.528
552	ARG78	NE	-19.848	9.81	13.932
553	ARG78	CZ	-19.36	11.053	13.921
554	ARG78	NH1	-18.114	11.278	13.497
555	ARG78	NH2	-20.12	12.072	14.33
556	GLN79	N	-21.028	7.577	18.722
557	GLN79	CA	-21.128	8.129	20.088
558	GLN79	C	-22.484	7.818	20.715
559	GLN79	O	-23.48	8.503	20.45
560	GLN79	CB	-20.937	9.651	20.09
561	GLN79	CG	-19.486	10.085	19.884
562	GLN79	CD	-19.353	11.607	19.931
563	GLN79	OE1	-19.071	12.193	20.986
564	GLN79	NE2	-19.508	12.226	18.773
565	ILE80	N	-22.504	6.806	21.562
566	ILE80	CA	-23.733	6.44	22.273
567	ILE80	C	-23.732	7.034	23.679
568	ILE80	O	-22.666	7.316	24.24
569	ILE80	CB	-23.847	4.919	22.333
570	ILE80	CG1	-22.684	4.305	23.109
571	ILE80	CG2	-23.905	4.35	20.92
572	ILE80	CD1	-22.794	2.788	23.191
573	ARG81	N	-24.932	7.278	24.188
574	ARG81	CA	-25.15	7.84	25.535
575	ARG81	C	-24.657	9.276	25.691
576	ARG81	O	-23.493	9.571	25.411
577	ARG81	CB	-24.51	6.964	26.603
578	ARG81	CG	-25.437	5.843	27.046
579	ARG81	CD	-25.685	5.92	28.555
580	ARG81	NE	-26.269	7.22	28.93
581	ARG81	CZ	-25.651	8.095	29.722
582	ARG81	NH1	-24.439	7.82	30.204
583	ARG81	NH2	-26.234	9.257	30.008
584	ARG82	N	-25.448	10.076	26.389
585	ARG82	CA	-25.192	11.523	26.511
586	ARG82	C	-23.872	11.866	27.204
587	ARG82	O	-23.108	12.684	26.682
588	ARG82	CB	-26.32	12.122	27.333
589	ARG82	CG	-27.683	11.796	26.74
590	ARG82	CD	-28.801	12.301	27.643
591	ARG82	NE	-28.71	11.659	28.967
592	ARG82	CZ	-28.623	12.34	30.114

593	ARG82	NH1	-28.477	11.689	31.271
594	ARG82	NH2	-28.606	13.675	30.096
595	GLU83	N	-23.495	11.077	28.198
596	GLU83	CA	-22.237	11.334	28.909
597	GLU83	C	-21.03	10.69	28.227
598	GLU83	O	-19.894	10.902	28.657
599	GLU83	CB	-22.361	10.828	30.338
600	GLU83	CG	-23.385	11.651	31.114
601	GLU83	CD	-23.478	11.172	32.56
602	GLU83	OE1	-23.428	9.967	32.761
603	GLU83	OE2	-23.71	12.011	33.418
604	ASP84	N	-21.274	9.941	27.165
605	ASP84	CA	-20.201	9.327	26.386
606	ASP84	C	-20.095	10.012	25.024
607	ASP84	O	-19.257	9.646	24.19
608	ASP84	CB	-20.481	7.841	26.237
609	ASP84	CG	-20.585	7.191	27.613
610	ASP84	OD1	-19.547	6.906	28.193
611	ASP84	OD2	-21.704	7.048	28.092
612	LYS85	N	-20.939	11.017	24.831
613	LYS85	CA	-20.846	11.928	23.681
614	LYS85	C	-19.997	13.228	23.804
615	LYS85	O	-20.236	14.084	22.942
616	LYS85	CB	-22.27	12.347	23.327
617	LYS85	CG	-23.107	11.173	22.832
618	LYS85	CD	-24.573	11.567	22.679
619	LYS85	CE	-25.408	10.408	22.148
620	LYS85	NZ	-26.824	10.785	22.036
621	PRO86	N	-19.054	13.455	24.73
622	PRO86	CA	-18.316	14.731	24.698
623	PRO86	C	-17.168	14.8	23.679
624	PRO86	O	-16.339	15.713	23.772
625	PRO86	CB	-17.779	14.922	26.08
626	PRO86	CG	-17.866	13.6	26.815
627	PRO86	CD	-18.543	12.646	25.852
628	PHE87	N	-17.14	13.906	22.701
629	PHE87	CA	-16.12	13.963	21.653
630	PHE87	C	-16.67	14.817	20.51
631	PHE87	O	-15.963	15.16	19.559
632	PHE87	CB	-15.848	12.556	21.128
633	PHE87	CG	-15.724	11.449	22.174
634	PHE87	CD1	-16.447	10.277	21.996
635	PHE87	CD2	-14.904	11.591	23.286
636	PHE87	CE1	-16.358	9.254	22.93
637	PHE87	CE2	-14.817	10.567	24.22
638	PHE87	CZ	-15.544	9.399	24.044
639	ARG88	N	-17.948	15.143	20.627
640	ARG88	CA	-18.629	16.037	19.686
641	ARG88	C	-18.178	17.519	19.7
642	ARG88	O	-18.118	18.064	18.59
643	ARG88	CB	-20.122	15.915	19.965
644	ARG88	CG	-20.964	16.678	18.953
645	ARG88	CD	-22.429	16.294	19.089
646	ARG88	NE	-22.593	14.851	18.868

647	ARG88	CZ	-23.307	14.07	19.679
648	ARG88	NH1	-23.373	12.757	19.45
649	ARG88	NH2	-23.922	14.598	20.739
650	PRO89	N	-17.919	18.194	20.826
651	PRO89	CA	-17.186	19.48	20.763
652	PRO89	C	-15.737	19.333	20.277
653	PRO89	O	-14.786	19.454	21.057
654	PRO89	CB	-17.206	20.033	22.154
655	PRO89	CG	-17.798	19.004	23.096
656	PRO89	CD	-18.208	17.832	22.224
657	SER90	N	-15.606	19.29	18.963
658	SER90	CA	-14.334	19.04	18.296
659	SER90	C	-14.43	19.413	16.824
660	SER90	O	-15.534	19.592	16.293
661	SER90	CB	-14.069	17.55	18.375
662	SER90	OG	-15.095	16.928	17.609
663	LEU91	N	-13.326	19.173	16.14
664	LEU91	CA	-13.154	19.564	14.737
665	LEU91	C	-14.042	18.804	13.745
666	LEU91	O	-14.491	19.39	12.754
667	LEU91	CB	-11.702	19.238	14.405
668	LEU91	CG	-11.325	19.637	12.988
669	LEU91	CD1	-11.253	21.153	12.877
670	LEU91	CD2	-9.989	19.012	12.606
671	ILE92	N	-14.422	17.582	14.076
672	ILE92	CA	-15.199	16.791	13.12
673	ILE92	C	-16.712	16.857	13.368
674	ILE92	O	-17.487	16.497	12.474
675	ILE92	CB	-14.682	15.351	13.173
676	ILE92	CG1	-15.288	14.488	12.07
677	ILE92	CG2	-14.932	14.719	14.539
678	ILE92	CD1	-14.775	13.055	12.137
679	ALA93	N	-17.14	17.407	14.494
680	ALA93	CA	-18.578	17.414	14.759
681	ALA93	C	-19.15	18.822	14.872
682	ALA93	O	-20.335	19.048	14.589
683	ALA93	CB	-18.865	16.593	16.004
684	MET94	N	-18.294	19.776	15.191
685	MET94	CA	-18.739	21.168	15.216
686	MET94	C	-18.99	21.683	13.811
687	MET94	O	-18.221	21.436	12.88
688	MET94	CB	-17.695	22.042	15.893
689	MET94	CG	-17.822	21.982	17.407
690	MET94	SD	-16.686	23.058	18.31
691	MET94	CE	-17.561	23.095	19.891
692	ASP95	N	-20.089	22.398	13.672
693	ASP95	CA	-20.42	23.024	12.393
694	ASP95	C	-19.831	24.427	12.371
695	ASP95	O	-19.589	25.001	13.438
696	ASP95	CB	-21.938	23.082	12.258
697	ASP95	CG	-22.52	21.677	12.373
698	ASP95	OD1	-22.276	20.87	11.484
699	ASP95	OD2	-23.173	21.412	13.37
700	PRO96	N	-19.488	24.936	11.201

701	PRO96	CA	-19.076	26.343	11.099
702	PRO96	C	-20.177	27.263	11.641
703	PRO96	O	-21.353	26.892	11.581
704	PRO96	CB	-18.812	26.567	9.64
705	PRO96	CG	-19.078	25.278	8.875
706	PRO96	CD	-19.532	24.256	9.905
707	PRO97	N	-19.817	28.38	12.263
708	PRO97	CA	-18.428	28.85	12.436
709	PRO97	C	-17.649	28.271	13.631
710	PRO97	O	-16.462	28.595	13.772
711	PRO97	CB	-18.567	30.329	12.615
712	PRO97	CG	-20.013	30.649	12.964
713	PRO97	CD	-20.777	29.345	12.804
714	GLU98	N	-18.233	27.353	14.389
715	GLU98	CA	-17.555	26.761	15.556
716	GLU98	C	-16.353	25.946	15.099
717	GLU98	O	-15.224	26.174	15.555
718	GLU98	CB	-18.513	25.782	16.223
719	GLU98	CG	-19.894	26.372	16.474
720	GLU98	CD	-20.857	25.236	16.811
721	GLU98	OE1	-20.697	24.171	16.227
722	GLU98	OE2	-21.799	25.49	17.544
723	HIS99	N	-16.575	25.223	14.013
724	HIS99	CA	-15.52	24.448	13.359
725	HIS99	C	-14.43	25.323	12.743
726	HIS99	O	-13.249	24.993	12.887
727	HIS99	CB	-16.19	23.646	12.252
728	HIS99	CG	-15.238	23.09	11.22
729	HIS99	ND1	-14.522	21.957	11.317
730	HIS99	CD2	-14.946	23.649	9.998
731	HIS99	CE1	-13.779	21.805	10.203
732	HIS99	NE2	-14.042	22.852	9.39
733	GLY100	N	-14.792	26.524	12.322
734	GLY100	CA	-13.832	27.439	11.702
735	GLY100	C	-12.859	27.944	12.756
736	GLY100	O	-11.648	27.716	12.64
737	LYS101	N	-13.419	28.385	13.872
738	LYS101	CA	-12.626	28.895	14.993
739	LYS101	C	-11.711	27.823	15.579
740	LYS101	O	-10.485	28.02	15.622
741	LYS101	CB	-13.608	29.33	16.07
742	LYS101	CG	-12.893	29.892	17.291
743	LYS101	CD	-13.829	29.939	18.492
744	LYS101	CE	-14.189	28.531	18.955
745	LYS101	NZ	-12.986	27.796	19.381
746	ALA102	N	-12.251	26.624	15.738
747	ALA102	CA	-11.474	25.523	16.313
748	ALA102	C	-10.381	25.022	15.373
749	ALA102	O	-9.243	24.859	15.828
750	ALA102	CB	-12.425	24.379	16.645
751	ARG103	N	-10.622	25.091	14.074
752	ARG103	CA	-9.63	24.64	13.097
753	ARG103	C	-8.492	25.644	12.958
754	ARG103	O	-7.325	25.236	13.033

755	ARG103	CB	-10.347	24.476	11.762
756	ARG103	CG	-9.496	23.785	10.705
757	ARG103	CD	-10.366	23.455	9.496
758	ARG103	NE	-9.651	22.682	8.467
759	ARG103	CZ	-9.807	21.367	8.287
760	ARG103	NH1	-10.493	20.645	9.175
761	ARG103	NH2	-9.174	20.755	7.285
762	ARG104	N	-8.811	26.923	13.087
763	ARG104	CA	-7.775	27.957	13.006
764	ARG104	C	-6.906	27.966	14.256
765	ARG104	O	-5.675	28.083	14.149
766	ARG104	CB	-8.442	29.316	12.84
767	ARG104	CG	-9.166	29.412	11.502
768	ARG104	CD	-9.828	30.772	11.319
769	ARG104	NE	-10.874	30.999	12.329
770	ARG104	CZ	-11.061	32.171	12.941
771	ARG104	NH1	-10.231	33.188	12.701
772	ARG104	NH2	-12.048	32.31	13.829
773	ASP105	N	-7.5	27.625	15.388
774	ASP105	CA	-6.718	27.493	16.616
775	ASP105	C	-5.828	26.253	16.594
776	ASP105	O	-4.602	26.392	16.716
777	ASP105	CB	-7.67	27.427	17.806
778	ASP105	CG	-8.198	28.814	18.165
779	ASP105	OD1	-7.389	29.588	18.666
780	ASP105	OD2	-9.411	28.938	18.257
781	VAL106	N	-6.379	25.125	16.173
782	VAL106	CA	-5.636	23.86	16.236
783	VAL106	C	-4.51	23.761	15.214
784	VAL106	O	-3.414	23.348	15.612
785	VAL106	CB	-6.611	22.703	16.046
786	VAL106	CG1	-5.886	21.37	15.89
787	VAL106	CG2	-7.587	22.637	17.212
788	VAL107	N	-4.641	24.427	14.075
789	VAL107	CA	-3.565	24.397	13.071
790	VAL107	C	-2.362	25.259	13.474
791	VAL107	O	-1.225	24.918	13.123
792	VAL107	CB	-4.142	24.869	11.737
793	VAL107	CG1	-3.06	25.104	10.687
794	VAL107	CG2	-5.175	23.879	11.213
795	GLY108	N	-2.576	26.155	14.426
796	GLY108	CA	-1.49	26.985	14.953
797	GLY108	C	-0.511	26.183	15.813
798	GLY108	O	0.685	26.491	15.837
799	GLU109	N	-1.006	25.191	16.537
800	GLU109	CA	-0.109	24.388	17.376
801	GLU109	C	0.121	22.976	16.836
802	GLU109	O	1.086	22.311	17.229
803	GLU109	CB	-0.677	24.35	18.784
804	GLU109	CG	-0.577	25.728	19.424
805	GLU109	CD	0.886	26.1	19.659
806	GLU109	OE1	1.612	25.244	20.147
807	GLU109	OE2	1.22	27.255	19.442
808	PHE110	N	-0.686	22.572	15.873

809	PHE110	CA	-0.511	21.269	15.221
810	PHE110	C	0.017	21.468	13.798
811	PHE110	O	-0.547	20.963	12.819
812	PHE110	CB	-1.866	20.568	15.206
813	PHE110	CG	-1.834	19.088	14.838
814	PHE110	CD1	-0.842	18.264	15.352
815	PHE110	CD2	-2.808	18.564	13.998
816	PHE110	CE1	-0.819	16.915	15.019
817	PHE110	CE2	-2.784	17.216	13.665
818	PHE110	CZ	-1.79	16.392	14.176
819	THR111	N	1.103	22.217	13.706
820	THR111	CA	1.68	22.585	12.409
821	THR111	C	2.353	21.411	11.71
822	THR111	O	2.846	20.47	12.346
823	THR111	CB	2.745	23.65	12.628
824	THR111	OG1	3.887	23.019	13.193
825	THR111	CG2	2.27	24.756	13.561
826	VAL112	N	2.564	21.605	10.417
827	VAL112	CA	3.302	20.63	9.605
828	VAL112	C	4.802	20.712	9.887
829	VAL112	O	5.492	19.689	9.86
830	VAL112	CB	3.026	20.929	8.134
831	VAL112	CG1	3.819	20.01	7.21
832	VAL112	CG2	1.535	20.833	7.832
833	LYS113	N	5.227	21.845	10.425
834	LYS113	CA	6.608	22.003	10.884
835	LYS113	C	6.892	21.096	12.082
836	LYS113	O	7.864	20.332	12.044
837	LYS113	CB	6.795	23.456	11.298
838	LYS113	CG	8.168	23.696	11.914
839	LYS113	CD	8.232	25.064	12.582
840	LYS113	CE	7.189	25.184	13.692
841	LYS113	NZ	7.407	24.178	14.747
842	ARG114	N	5.945	21.013	13.008
843	ARG114	CA	6.085	20.094	14.141
844	ARG114	C	6.098	18.627	13.713
845	ARG114	O	7.034	17.912	14.09
846	ARG114	CB	4.916	20.313	15.096
847	ARG114	CG	4.939	19.283	16.22
848	ARG114	CD	3.721	19.388	17.131
849	ARG114	NE	3.696	20.666	17.858
850	ARG114	CZ	4.078	20.792	19.131
851	ARG114	NH1	3.903	21.953	19.766
852	ARG114	NH2	4.537	19.73	19.798
853	MET115	N	5.28	18.265	12.737
854	MET115	CA	5.23	16.862	12.311
855	MET115	C	6.438	16.467	11.456
856	MET115	O	6.99	15.378	11.662
857	MET115	CB	3.926	16.642	11.555
858	MET115	CG	2.739	16.915	12.474
859	MET115	SD	1.093	16.637	11.78
860	MET115	CE	1.057	17.94	10.532
861	LYS116	N	7.027	17.445	10.787
862	LYS116	CA	8.25	17.222	10.01

863	LYS116	C	9.492	17.156	10.902
864	LYS116	O	10.434	16.413	10.59
865	LYS116	CB	8.372	18.392	9.042
866	LYS116	CG	9.635	18.337	8.194
867	LYS116	CD	9.738	19.592	7.338
868	LYS116	CE	9.703	20.841	8.213
869	LYS116	NZ	9.753	22.063	7.395
870	ALA117	N	9.404	17.748	12.084
871	ALA117	CA	10.49	17.663	13.066
872	ALA117	C	10.354	16.43	13.962
873	ALA117	O	11.331	16	14.587
874	ALA117	CB	10.469	18.924	13.922
875	LEU118	N	9.185	15.81	13.933
876	LEU118	CA	8.975	14.544	14.64
877	LEU118	C	9.351	13.359	13.76
878	LEU118	O	9.591	12.26	14.275
879	LEU118	CB	7.512	14.434	15.05
880	LEU118	CG	7.153	15.474	16.104
881	LEU118	CD1	5.654	15.48	16.372
882	LEU118	CD2	7.934	15.246	17.393
883	GLN119	N	9.563	13.632	12.483
884	GLN119	CA	10.052	12.633	11.518
885	GLN119	C	11.263	11.797	11.989
886	GLN119	O	11.09	10.573	12.041
887	GLN119	CB	10.378	13.373	10.227
888	GLN119	CG	10.944	12.471	9.144
889	GLN119	CD	11.394	13.351	7.985
890	GLN119	OE1	11.701	12.857	6.894
891	GLN119	NE2	11.444	14.647	8.243
892	PRO120	N	12.388	12.361	12.439
893	PRO120	CA	13.485	11.486	12.885
894	PRO120	C	13.211	10.732	14.195
895	PRO120	O	13.761	9.639	14.381
896	PRO120	CB	14.672	12.386	13.05
897	PRO120	CG	14.237	13.832	12.892
898	PRO120	CD	12.764	13.785	12.533
899	ARG121	N	12.229	11.159	14.974
900	ARG121	CA	11.917	10.438	16.203
901	ARG121	C	11.02	9.25	15.868
902	ARG121	O	11.331	8.136	16.303
903	ARG121	CB	11.218	11.385	17.174
904	ARG121	CG	11.741	11.209	18.597
905	ARG121	CD	11.481	9.812	19.149
906	ARG121	NE	12.184	9.613	20.424
907	ARG121	CZ	12.714	8.443	20.784
908	ARG121	NH1	13.415	8.346	21.915
909	ARG121	NH2	12.601	7.386	19.977
910	ILE122	N	10.18	9.421	14.857
911	ILE122	CA	9.316	8.332	14.381
912	ILE122	C	10.135	7.27	13.656
913	ILE122	O	9.975	6.073	13.928
914	ILE122	CB	8.309	8.918	13.396
915	ILE122	CG1	7.456	9.995	14.052
916	ILE122	CG2	7.422	7.825	12.807

917	ILE122	CD1	6.509	10.636	13.044
918	GLN123	N	11.179	7.724	12.982
919	GLN123	CA	12.088	6.827	12.269
920	GLN123	C	12.914	5.997	13.245
921	GLN123	O	12.897	4.76	13.156
922	GLN123	CB	12.989	7.717	11.423
923	GLN123	CG	13.978	6.941	10.567
924	GLN123	CD	14.72	7.939	9.684
925	GLN123	OE1	15.954	7.96	9.626
926	GLN123	NE2	13.946	8.8	9.044
927	GLN124	N	13.295	6.633	14.34
928	GLN124	CA	14.049	5.959	15.394
929	GLN124	C	13.184	4.947	16.144
930	GLN124	O	13.621	3.798	16.284
931	GLN124	CB	14.544	7.04	16.345
932	GLN124	CG	15.429	6.495	17.455
933	GLN124	CD	15.912	7.668	18.3
934	GLN124	OE1	16.786	7.524	19.162
935	GLN124	NE2	15.357	8.832	18.008
936	ILE125	N	11.904	5.252	16.299
937	ILE125	CA	10.961	4.328	16.947
938	ILE125	C	10.716	3.072	16.112
939	ILE125	O	10.861	1.961	16.642
940	ILE125	CB	9.638	5.064	17.148
941	ILE125	CG1	9.792	6.214	18.13
942	ILE125	CG2	8.543	4.122	17.628
943	ILE125	CD1	8.487	6.984	18.275
944	VAL126	N	10.649	3.229	14.797
945	VAL126	CA	10.44	2.064	13.928
946	VAL126	C	11.693	1.2	13.87
947	VAL126	O	11.603	-0.021	14.062
948	VAL126	CB	10.119	2.529	12.513
949	VAL126	CG1	9.754	1.334	11.641
950	VAL126	CG2	8.988	3.544	12.503
951	ASP127	N	12.843	1.855	13.909
952	ASP127	CA	14.121	1.141	13.889
953	ASP127	C	14.314	0.34	15.17
954	ASP127	O	14.537	-0.876	15.088
955	ASP127	CB	15.258	2.153	13.769
956	ASP127	CG	15.158	2.967	12.481
957	ASP127	OD1	15.632	4.097	12.49
958	ASP127	OD2	14.686	2.426	11.489
959	GLU128	N	13.903	0.919	16.288
960	GLU128	CA	14.048	0.26	17.589
961	GLU128	C	13.094	-0.915	17.762
962	GLU128	O	13.527	-1.952	18.281
963	GLU128	CB	13.764	1.281	18.684
964	GLU128	CG	14.807	2.39	18.707
965	GLU128	CD	14.367	3.489	19.668
966	GLU128	OE1	13.584	4.333	19.247
967	GLU128	OE2	14.794	3.452	20.812
968	HIS129	N	11.934	-0.861	17.128
969	HIS129	CA	11.002	-1.985	17.237
970	HIS129	C	11.411	-3.142	16.333

971	HIS129	O	11.344	-4.297	16.772
972	HIS129	CB	9.592	-1.533	16.885
973	HIS129	CG	8.963	-0.57	17.87
974	HIS129	ND1	7.942	0.266	17.612
975	HIS129	CD2	9.3	-0.394	19.192
976	HIS129	CE1	7.647	0.969	18.724
977	HIS129	NE2	8.488	0.561	19.701
978	ILE130	N	12.061	-2.848	15.218
979	ILE130	CA	12.564	-3.95	14.394
980	ILE130	C	13.768	-4.577	15.089
981	ILE130	O	13.69	-5.756	15.459
982	ILE130	CB	12.968	-3.449	13.012
983	ILE130	CG1	11.841	-2.659	12.36
984	ILE130	CG2	13.341	-4.632	12.125
985	ILE130	CD1	12.258	-2.117	10.996
986	ASP131	N	14.65	-3.712	15.575
987	ASP131	CA	15.874	-4.12	16.283
988	ASP131	C	15.604	-5.033	17.473
989	ASP131	O	15.932	-6.226	17.435
990	ASP131	CB	16.565	-2.874	16.84
991	ASP131	CG	17.175	-1.999	15.749
992	ASP131	OD1	17.222	-0.791	15.952
993	ASP131	OD2	17.743	-2.564	14.826
994	ALA132	N	14.882	-4.505	18.448
995	ALA132	CA	14.708	-5.198	19.727
996	ALA132	C	13.582	-6.228	19.763
997	ALA132	O	13.489	-6.983	20.738
998	ALA132	CB	14.465	-4.147	20.803
999	LEU133	N	12.752	-6.286	18.736
1000	LEU133	CA	11.712	-7.311	18.741
1001	LEU133	C	12.08	-8.444	17.798
1002	LEU133	O	12.567	-9.492	18.239
1003	LEU133	CB	10.366	-6.697	18.372
1004	LEU133	CG	9.925	-5.686	19.427
1005	LEU133	CD1	8.679	-4.93	18.987
1006	LEU133	CD2	9.698	-6.366	20.773
1007	LEU134	N	11.901	-8.215	16.511
1008	LEU134	CA	12.139	-9.288	15.539
1009	LEU134	C	12.895	-8.777	14.32
1010	LEU134	O	12.319	-8.632	13.237
1011	LEU134	CB	10.808	-9.885	15.087
1012	LEU134	CG	10.481	-11.234	15.731
1013	LEU134	CD1	11.66	-12.193	15.635
1014	LEU134	CD2	9.997	-11.115	17.173
1015	ALA135	N	14.194	-8.586	14.486
1016	ALA135	CA	15.038	-8.142	13.371
1017	ALA135	C	15.606	-9.293	12.538
1018	ALA135	O	16.184	-9.051	11.472
1019	ALA135	CB	16.193	-7.323	13.935
1020	GLY136	N	15.402	-10.522	12.984
1021	GLY136	CA	15.957	-11.679	12.272
1022	GLY136	C	14.865	-12.524	11.62
1023	GLY136	O	14.069	-12.022	10.829
1024	PRO137	N	14.906	-13.813	11.903

1025	PRO137	CA	13.938	-14.772	11.353
1026	PRO137	C	12.589	-14.709	12.067
1027	PRO137	O	12.21	-13.679	12.637
1028	PRO137	CB	14.573	-16.111	11.568
1029	PRO137	CG	15.748	-15.953	12.524
1030	PRO137	CD	15.899	-14.46	12.763
1031	LYS138	N	11.86	-15.811	11.945
1032	LYS138	CA	10.575	-16.043	12.639
1033	LYS138	C	9.412	-15.227	12.069
1034	LYS138	O	9.605	-14.143	11.508
1035	LYS138	CB	10.733	-15.765	14.135
1036	LYS138	CG	11.795	-16.66	14.765
1037	LYS138	CD	12.022	-16.303	16.23
1038	LYS138	CE	13.155	-17.128	16.829
1039	LYS138	NZ	12.859	-18.567	16.746
1040	PRO139	N	8.256	-15.868	12.022
1041	PRO139	CA	6.996	-15.155	11.797
1042	PRO139	C	6.612	-14.289	12.995
1043	PRO139	O	6.167	-14.795	14.031
1044	PRO139	CB	5.979	-16.232	11.583
1045	PRO139	CG	6.595	-17.575	11.948
1046	PRO139	CD	8.04	-17.286	12.322
1047	ALA140	N	6.749	-12.987	12.824
1048	ALA140	CA	6.355	-12.036	13.868
1049	ALA140	C	5.006	-11.411	13.552
1050	ALA140	O	4.591	-11.359	12.391
1051	ALA140	CB	7.395	-10.931	13.953
1052	ASP141	N	4.297	-10.989	14.582
1053	ASP141	CA	3.051	-10.264	14.336
1054	ASP141	C	3.363	-8.779	14.165
1055	ASP141	O	3.466	-8.032	15.149
1056	ASP141	CB	2.073	-10.492	15.481
1057	ASP141	CG	0.741	-9.84	15.132
1058	ASP141	OD1	0.583	-8.673	15.465
1059	ASP141	OD2	0.016	-10.426	14.338
1060	LEU142	N	3.261	-8.332	12.923
1061	LEU142	CA	3.692	-6.983	12.541
1062	LEU142	C	2.753	-5.893	13.048
1063	LEU142	O	3.232	-4.806	13.4
1064	LEU142	CB	3.78	-6.96	11.012
1065	LEU142	CG	4.336	-5.66	10.428
1066	LEU142	CD1	5.227	-5.944	9.225
1067	LEU142	CD2	3.241	-4.659	10.063
1068	VAL143	N	1.509	-6.243	13.329
1069	VAL143	CA	0.585	-5.247	13.868
1070	VAL143	C	0.992	-4.867	15.287
1071	VAL143	O	1.481	-3.748	15.477
1072	VAL143	CB	-0.829	-5.809	13.859
1073	VAL143	CG1	-1.823	-4.772	14.374
1074	VAL143	CG2	-1.212	-6.26	12.457
1075	GLN144	N	1.184	-5.874	16.119
1076	GLN144	CA	1.491	-5.656	17.535
1077	GLN144	C	2.945	-5.249	17.797
1078	GLN144	O	3.212	-4.566	18.791

1079	GLN144	CB	1.203	-6.982	18.23
1080	GLN144	CG	1.485	-6.966	19.726
1081	GLN144	CD	1.232	-8.364	20.277
1082	GLN144	OE1	1.815	-8.777	21.285
1083	GLN144	NE2	0.374	-9.091	19.582
1084	ALA145	N	3.842	-5.539	16.87
1085	ALA145	CA	5.246	-5.186	17.088
1086	ALA145	C	5.672	-3.884	16.412
1087	ALA145	O	6.594	-3.211	16.888
1088	ALA145	CB	6.108	-6.329	16.561
1089	LEU146	N	4.988	-3.499	15.349
1090	LEU146	CA	5.424	-2.324	14.588
1091	LEU146	C	4.294	-1.342	14.317
1092	LEU146	O	4.308	-0.207	14.815
1093	LEU146	CB	5.964	-2.825	13.252
1094	LEU146	CG	7.225	-3.659	13.433
1095	LEU146	CD1	7.467	-4.589	12.254
1096	LEU146	CD2	8.432	-2.772	13.705
1097	SER147	N	3.245	-1.868	13.71
1098	SER147	CA	2.169	-1.053	13.134
1099	SER147	C	1.274	-0.369	14.164
1100	SER147	O	0.727	0.708	13.911
1101	SER147	CB	1.325	-2.001	12.301
1102	SER147	OG	0.198	-1.277	11.856
1103	LEU148	N	1.174	-0.97	15.331
1104	LEU148	CA	0.484	-0.358	16.464
1105	LEU148	C	1.433	0.51	17.316
1106	LEU148	O	1.132	1.707	17.436
1107	LEU148	CB	-0.204	-1.475	17.259
1108	LEU148	CG	-1.13	-0.987	18.372
1109	LEU148	CD1	-2.317	-1.93	18.53
1110	LEU148	CD2	-0.404	-0.81	19.703
1111	PRO149	N	2.553	0.008	17.848
1112	PRO149	CA	3.299	0.829	18.809
1113	PRO149	C	3.987	2.052	18.203
1114	PRO149	O	4.043	3.07	18.9
1115	PRO149	CB	4.31	-0.075	19.439
1116	PRO149	CG	4.261	-1.43	18.764
1117	PRO149	CD	3.122	-1.352	17.766
1118	VAL150	N	4.316	2.051	16.918
1119	VAL150	CA	4.873	3.276	16.323
1120	VAL150	C	3.867	4.442	16.385
1121	VAL150	O	4.127	5.334	17.201
1122	VAL150	CB	5.399	3.041	14.905
1123	VAL150	CG1	5.892	4.345	14.284
1124	VAL150	CG2	6.514	2.004	14.891
1125	PRO151	N	2.695	4.396	15.75
1126	PRO151	CA	1.816	5.574	15.799
1127	PRO151	C	1.187	5.843	17.167
1128	PRO151	O	1.009	7.014	17.532
1129	PRO151	CB	0.742	5.307	14.799
1130	PRO151	CG	0.88	3.895	14.266
1131	PRO151	CD	2.136	3.336	14.896
1132	SER152	N	1.059	4.817	17.993

1133	SER152	CA	0.504	5.027	19.326
1134	SER152	C	1.506	5.73	20.241
1135	SER152	O	1.136	6.724	20.879
1136	SER152	CB	0.117	3.671	19.898
1137	SER152	OG	-0.849	3.09	19.031
1138	LEU153	N	2.785	5.428	20.079
1139	LEU153	CA	3.817	6.088	20.883
1140	LEU153	C	4.17	7.458	20.312
1141	LEU153	O	4.34	8.406	21.091
1142	LEU153	CB	5.06	5.206	20.899
1143	LEU153	CG	6.168	5.789	21.769
1144	LEU153	CD1	5.708	5.934	23.216
1145	LEU153	CD2	7.424	4.928	21.689
1146	VAL154	N	3.995	7.622	19.009
1147	VAL154	CA	4.232	8.925	18.383
1148	VAL154	C	3.185	9.944	18.813
1149	VAL154	O	3.566	11.036	19.256
1150	VAL154	CB	4.205	8.777	16.864
1151	VAL154	CG1	4.148	10.134	16.169
1152	VAL154	CG2	5.402	7.976	16.368
1153	ILE155	N	1.945	9.513	18.977
1154	ILE155	CA	0.935	10.467	19.431
1155	ILE155	C	0.932	10.621	20.956
1156	ILE155	O	0.6	11.709	21.446
1157	ILE155	CB	-0.433	10.065	18.902
1158	ILE155	CG1	-1.405	11.218	19.089
1159	ILE155	CG2	-0.956	8.814	19.593
1160	ILE155	CD1	-0.954	12.46	18.327
1161	CYS156	N	1.569	9.697	21.66
1162	CYS156	CA	1.787	9.891	23.093
1163	CYS156	C	2.835	10.973	23.317
1164	CYS156	O	2.551	11.93	24.047
1165	CYS156	CB	2.261	8.59	23.732
1166	CYS156	SG	1.018	7.295	23.935
1167	GLU157	N	3.838	11.005	22.454
1168	GLU157	CA	4.902	12.011	22.559
1169	GLU157	C	4.512	13.364	21.957
1170	GLU157	O	5.08	14.393	22.339
1171	GLU157	CB	6.109	11.474	21.801
1172	GLU157	CG	6.57	10.14	22.372
1173	GLU157	CD	7.588	9.499	21.434
1174	GLU157	OE1	8.764	9.522	21.767
1175	GLU157	OE2	7.162	8.932	20.437
1176	LEU158	N	3.5	13.37	21.107
1177	LEU158	CA	3.042	14.616	20.492
1178	LEU158	C	2.03	15.308	21.401
1179	LEU158	O	2.089	16.535	21.586
1180	LEU158	CB	2.412	14.232	19.14
1181	LEU158	CG	2.171	15.389	18.175
1182	LEU158	CD1	2.086	14.868	16.745
1183	LEU158	CD2	0.93	16.213	18.504
1184	LEU159	N	1.211	14.518	22.072
1185	LEU159	CA	0.183	15.099	22.929
1186	LEU159	C	0.747	15.411	24.309

1187	LEU159	O	0.832	16.594	24.66
1188	LEU159	CB	-0.979	14.12	23.044
1189	LEU159	CG	-2.24	14.827	23.524
1190	LEU159	CD1	-2.637	15.915	22.535
1191	LEU159	CD2	-3.385	13.84	23.707
1192	GLY160	N	1.347	14.417	24.943
1193	GLY160	CA	1.874	14.572	26.306
1194	GLY160	C	1.433	13.413	27.2
1195	GLY160	O	1.183	13.581	28.398
1196	VAL161	N	1.366	12.238	26.601
1197	VAL161	CA	0.869	11.037	27.284
1198	VAL161	C	2.006	10.078	27.635
1199	VAL161	O	2.715	9.58	26.752
1200	VAL161	CB	-0.111	10.348	26.338
1201	VAL161	CG1	-0.763	9.125	26.976
1202	VAL161	CG2	-1.175	11.327	25.866
1203	PRO162	N	2.15	9.806	28.922
1204	PRO162	CA	3.13	8.826	29.4
1205	PRO162	C	2.838	7.41	28.901
1206	PRO162	O	1.68	7.021	28.689
1207	PRO162	CB	3.066	8.899	30.894
1208	PRO162	CG	1.972	9.874	31.302
1209	PRO162	CD	1.358	10.384	30.009
1210	TYR163	N	3.882	6.593	28.912
1211	TYR163	CA	3.793	5.209	28.41
1212	TYR163	C	3.104	4.257	29.393
1213	TYR163	O	2.72	3.153	29.002
1214	TYR163	CB	5.192	4.684	28.071
1215	TYR163	CG	6.111	4.367	29.254
1216	TYR163	CD1	6.895	5.363	29.826
1217	TYR163	CD2	6.181	3.067	29.743
1218	TYR163	CE1	7.726	5.066	30.898
1219	TYR163	CE2	7.011	2.768	30.815
1220	TYR163	CZ	7.78	3.77	31.392
1221	TYR163	OH	8.589	3.478	32.467
1222	SER164	N	2.806	4.747	30.589
1223	SER164	CA	2.007	3.992	31.561
1224	SER164	C	0.51	4.158	31.301
1225	SER164	O	-0.319	3.566	32
1226	SER164	CB	2.303	4.538	32.952
1227	SER164	OG	1.766	5.854	33.017
1228	ASP165	N	0.173	5.056	30.389
1229	ASP165	CA	-1.215	5.273	30.002
1230	ASP165	C	-1.445	4.619	28.649
1231	ASP165	O	-2.542	4.126	28.344
1232	ASP165	CB	-1.463	6.775	29.944
1233	ASP165	CG	-1.331	7.38	31.343
1234	ASP165	OD1	-2.358	7.592	31.968
1235	ASP165	OD2	-0.21	7.683	31.732
1236	HIS166	N	-0.343	4.475	27.929
1237	HIS166	CA	-0.299	3.666	26.71
1238	HIS166	C	-0.63	2.223	27.09
1239	HIS166	O	-0.515	1.86	28.266
1240	HIS166	CB	1.11	3.792	26.129

1241	HIS166	CG	1.387	3.018	24.856
1242	HIS166	ND1	0.916	3.295	23.626
1243	HIS166	CD2	2.174	1.896	24.741
1244	HIS166	CE1	1.378	2.374	22.756
1245	HIS166	NE2	2.156	1.51	23.445
1246	GLU167	N	-1.239	1.506	26.155
1247	GLU167	CA	-1.754	0.127	26.342
1248	GLU167	C	-3.12	0.07	27.045
1249	GLU167	O	-4.04	-0.549	26.498
1250	GLU167	CB	-0.743	-0.752	27.077
1251	GLU167	CG	0.54	-0.919	26.271
1252	GLU167	CD	1.593	-1.638	27.107
1253	GLU167	OE1	1.207	-2.478	27.907
1254	GLU167	OE2	2.766	-1.386	26.875
1255	PHE168	N	-3.329	0.846	28.097
1256	PHE168	CA	-4.652	0.854	28.729
1257	PHE168	C	-5.586	1.779	27.954
1258	PHE168	O	-6.692	1.36	27.587
1259	PHE168	CB	-4.53	1.304	30.179
1260	PHE168	CG	-5.824	1.165	30.977
1261	PHE168	CD1	-6.696	0.117	30.709
1262	PHE168	CD2	-6.126	2.078	31.979
1263	PHE168	CE1	-7.875	-0.01	31.432
1264	PHE168	CE2	-7.305	1.951	32.703
1265	PHE168	CZ	-8.18	0.908	32.428
1266	PHE169	N	-5.016	2.851	27.423
1267	PHE169	CA	-5.773	3.717	26.514
1268	PHE169	C	-5.944	3.029	25.162
1269	PHE169	O	-7.031	3.098	24.579
1270	PHE169	CB	-5.003	5.024	26.316
1271	PHE169	CG	-5.736	6.088	25.497
1272	PHE169	CD1	-6.361	7.145	26.147
1273	PHE169	CD2	-5.758	6.022	24.109
1274	PHE169	CE1	-7.037	8.111	25.413
1275	PHE169	CE2	-6.436	6.985	23.375
1276	PHE169	CZ	-7.082	8.028	24.027
1277	GLN170	N	-5.019	2.134	24.851
1278	GLN170	CA	-5.042	1.407	23.584
1279	GLN170	C	-6.148	0.359	23.564
1280	GLN170	O	-6.903	0.281	22.588
1281	GLN170	CB	-3.705	0.693	23.444
1282	GLN170	CG	-3.611	-0.121	22.163
1283	GLN170	CD	-3.411	0.818	20.985
1284	GLN170	OE1	-2.392	1.516	20.917
1285	GLN170	NE2	-4.408	0.885	20.125
1286	SER171	N	-6.372	-0.281	24.698
1287	SER171	CA	-7.424	-1.295	24.769
1288	SER171	C	-8.811	-0.665	24.856
1289	SER171	O	-9.706	-1.107	24.125
1290	SER171	CB	-7.171	-2.209	25.967
1291	SER171	OG	-7.132	-1.427	27.155
1292	CYS172	N	-8.906	0.511	25.457
1293	CYS172	CA	-10.204	1.184	25.525
1294	CYS172	C	-10.569	1.806	24.18

1295	CYS172	O	-11.691	1.593	23.703
1296	CYS172	CB	-10.149	2.266	26.593
1297	CYS172	SG	-9.817	1.701	28.277
1298	SER173	N	-9.559	2.253	23.453
1299	SER173	CA	-9.781	2.826	22.121
1300	SER173	C	-9.949	1.765	21.033
1301	SER173	O	-10.363	2.096	19.916
1302	SER173	CB	-8.612	3.741	21.775
1303	SER173	OG	-7.418	2.972	21.747
1304	SER174	N	-9.687	0.509	21.356
1305	SER174	CA	-10.001	-0.575	20.427
1306	SER174	C	-11.395	-1.133	20.713
1307	SER174	O	-12.128	-1.464	19.771
1308	SER174	CB	-8.949	-1.668	20.566
1309	SER174	OG	-7.691	-1.099	20.225
1310	ARG175	N	-11.85	-0.974	21.949
1311	ARG175	CA	-13.224	-1.373	22.294
1312	ARG175	C	-14.226	-0.342	21.787
1313	ARG175	O	-15.298	-0.72	21.298
1314	ARG175	CB	-13.371	-1.514	23.805
1315	ARG175	CG	-12.486	-2.622	24.36
1316	ARG175	CD	-12.761	-2.871	25.837
1317	ARG175	NE	-12.544	-1.662	26.646
1318	ARG175	CZ	-13.06	-1.512	27.869
1319	ARG175	NH1	-12.78	-0.421	28.584
1320	ARG175	NH2	-13.816	-2.478	28.397
1321	MET176	N	-13.739	0.876	21.611
1322	MET176	CA	-14.516	1.951	20.985
1323	MET176	C	-14.649	1.843	19.467
1324	MET176	O	-15.284	2.71	18.855
1325	MET176	CB	-13.806	3.259	21.259
1326	MET176	CG	-13.86	3.657	22.721
1327	MET176	SD	-13.036	5.228	23.009
1328	MET176	CE	-13.493	5.972	21.425
1329	LEU177	N	-14.036	0.846	18.853
1330	LEU177	CA	-14.184	0.676	17.411
1331	LEU177	C	-15.219	-0.388	17.059
1332	LEU177	O	-15.593	-0.533	15.886
1333	LEU177	CB	-12.836	0.29	16.827
1334	LEU177	CG	-11.824	1.426	16.9
1335	LEU177	CD1	-10.568	1.035	16.135
1336	LEU177	CD2	-12.4	2.713	16.32
1337	SER178	N	-15.706	-1.099	18.062
1338	SER178	CA	-16.693	-2.149	17.793
1339	SER178	C	-18.117	-1.673	18.08
1340	SER178	O	-18.628	-1.797	19.2
1341	SER178	CB	-16.344	-3.402	18.599
1342	SER178	OG	-16.323	-3.095	19.988
1343	ARG179	N	-18.765	-1.209	17.022
1344	ARG179	CA	-20.148	-0.697	17.082
1345	ARG179	C	-21.17	-1.832	17.192
1346	ARG179	O	-21.743	-2.266	16.187
1347	ARG179	CB	-20.4	0.027	15.768
1348	ARG179	CG	-19.286	1.01	15.431

1349	ARG179	CD	-19.098	1.114	13.922
1350	ARG179	NE	-18.628	-0.179	13.39
1351	ARG179	CZ	-19.337	-0.967	12.576
1352	ARG179	NH1	-18.903	-2.2	12.307
1353	ARG179	NH2	-20.546	-0.583	12.156
1354	GLU180	N	-21.375	-2.313	18.405
1355	GLU180	CA	-22.261	-3.454	18.627
1356	GLU180	C	-23.553	-3.038	19.318
1357	GLU180	O	-23.676	-1.923	19.833
1358	GLU180	CB	-21.517	-4.449	19.508
1359	GLU180	CG	-20.175	-4.838	18.899
1360	GLU180	CD	-19.442	-5.795	19.828
1361	GLU180	OE1	-20.124	-6.592	20.457
1362	GLU180	OE2	-18.219	-5.763	19.834
1363	VAL181	N	-24.492	-3.969	19.374
1364	VAL181	CA	-25.72	-3.744	20.147
1365	VAL181	C	-25.463	-4.084	21.616
1366	VAL181	O	-26.012	-3.452	22.525
1367	VAL181	CB	-26.823	-4.627	19.569
1368	VAL181	CG1	-28.119	-4.498	20.362
1369	VAL181	CG2	-27.062	-4.297	18.099
1370	THR182	N	-24.438	-4.897	21.822
1371	THR182	CA	-23.936	-5.215	23.166
1372	THR182	C	-22.767	-4.302	23.547
1373	THR182	O	-21.827	-4.739	24.222
1374	THR182	CB	-23.459	-6.664	23.183
1375	THR182	OG1	-22.348	-6.789	22.302
1376	THR182	CG2	-24.551	-7.622	22.719
1377	ALA183	N	-22.882	-3.025	23.214
1378	ALA183	CA	-21.777	-2.062	23.352
1379	ALA183	C	-21.585	-1.459	24.748
1380	ALA183	O	-21.031	-0.36	24.855
1381	ALA183	CB	-21.993	-0.933	22.352
1382	GLU184	N	-21.832	-2.224	25.799
1383	GLU184	CA	-21.706	-1.688	27.158
1384	GLU184	C	-20.242	-1.537	27.568
1385	GLU184	O	-19.888	-0.536	28.199
1386	GLU184	CB	-22.415	-2.636	28.117
1387	GLU184	CG	-22.387	-2.118	29.551
1388	GLU184	CD	-23.145	-3.086	30.454
1389	GLU184	OE1	-22.924	-3.047	31.655
1390	GLU184	OE2	-23.953	-3.832	29.917
1391	GLU185	N	-19.374	-2.344	26.978
1392	GLU185	CA	-17.936	-2.201	27.244
1393	GLU185	C	-17.307	-1.143	26.337
1394	GLU185	O	-16.294	-0.542	26.708
1395	GLU185	CB	-17.216	-3.541	27.073
1396	GLU185	CG	-17.189	-4.388	28.351
1397	GLU185	CD	-18.561	-4.959	28.705
1398	GLU185	OE1	-19.308	-5.237	27.774
1399	GLU185	OE2	-18.899	-4.953	29.879
1400	ARG186	N	-18.044	-0.74	25.316
1401	ARG186	CA	-17.607	0.339	24.434
1402	ARG186	C	-18.008	1.676	25.049

1403	ARG186	O	-17.213	2.624	25.056
1404	ARG186	CB	-18.317	0.135	23.103
1405	ARG186	CG	-17.936	1.175	22.064
1406	ARG186	CD	-18.718	0.942	20.779
1407	ARG186	NE	-18.234	1.82	19.708
1408	ARG186	CZ	-19.002	2.705	19.073
1409	ARG186	NH1	-20.296	2.816	19.386
1410	ARG186	NH2	-18.474	3.477	18.122
1411	MET187	N	-19.086	1.627	25.817
1412	MET187	CA	-19.545	2.775	26.601
1413	MET187	C	-18.651	2.978	27.82
1414	MET187	O	-18.251	4.113	28.111
1415	MET187	CB	-20.958	2.459	27.07
1416	MET187	CG	-21.569	3.594	27.88
1417	MET187	SD	-23.104	3.161	28.726
1418	MET187	CE	-23.995	2.43	27.333
1419	THR188	N	-18.13	1.874	28.332
1420	THR188	CA	-17.174	1.925	29.44
1421	THR188	C	-15.819	2.442	28.969
1422	THR188	O	-15.237	3.307	29.634
1423	THR188	CB	-17.013	0.516	30
1424	THR188	OG1	-18.274	0.091	30.499
1425	THR188	CG2	-16.011	0.473	31.149
1426	ALA189	N	-15.477	2.139	27.726
1427	ALA189	CA	-14.243	2.652	27.133
1428	ALA189	C	-14.333	4.147	26.838
1429	ALA189	O	-13.403	4.884	27.192
1430	ALA189	CB	-13.996	1.884	25.844
1431	PHE190	N	-15.518	4.605	26.461
1432	PHE190	CA	-15.762	6.042	26.26
1433	PHE190	C	-15.632	6.81	27.572
1434	PHE190	O	-14.815	7.736	27.678
1435	PHE190	CB	-17.194	6.258	25.773
1436	PHE190	CG	-17.566	5.772	24.375
1437	PHE190	CD1	-16.652	5.837	23.334
1438	PHE190	CD2	-18.848	5.293	24.139
1439	PHE190	CE1	-17.013	5.406	22.063
1440	PHE190	CE2	-19.208	4.861	22.871
1441	PHE190	CZ	-18.291	4.917	21.832
1442	GLU191	N	-16.281	6.297	28.605
1443	GLU191	CA	-16.292	6.969	29.908
1444	GLU191	C	-14.921	6.971	30.575
1445	GLU191	O	-14.432	8.05	30.936
1446	GLU191	CB	-17.28	6.233	30.802
1447	GLU191	CG	-17.348	6.853	32.193
1448	GLU191	CD	-18.28	6.023	33.069
1449	GLU191	OE1	-18.424	4.843	32.777
1450	GLU191	OE2	-18.894	6.597	33.957
1451	SER192	N	-14.202	5.866	30.453
1452	SER192	CA	-12.877	5.76	31.071
1453	SER192	C	-11.82	6.545	30.301
1454	SER192	O	-10.892	7.077	30.921
1455	SER192	CB	-12.467	4.291	31.126
1456	SER192	OG	-12.37	3.801	29.792

1457	LEU193	N	-12.082	6.827	29.036
1458	LEU193	CA	-11.152	7.64	28.256
1459	LEU193	C	-11.441	9.127	28.435
1460	LEU193	O	-10.514	9.943	28.377
1461	LEU193	CB	-11.243	7.218	26.798
1462	LEU193	CG	-9.95	6.547	26.343
1463	LEU193	CD1	-9.372	5.603	27.391
1464	LEU193	CD2	-10.117	5.842	25.003
1465	GLU194	N	-12.63	9.438	28.923
1466	GLU194	CA	-12.93	10.811	29.327
1467	GLU194	C	-12.368	11.096	30.711
1468	GLU194	O	-11.82	12.182	30.938
1469	GLU194	CB	-14.437	11.017	29.337
1470	GLU194	CG	-14.97	11.164	27.922
1471	GLU194	CD	-14.35	12.405	27.287
1472	GLU194	OE1	-13.524	12.237	26.403
1473	GLU194	OE2	-14.826	13.487	27.596
1474	ASN195	N	-12.26	10.058	31.523
1475	ASN195	CA	-11.645	10.215	32.844
1476	ASN195	C	-10.126	10.268	32.715
1477	ASN195	O	-9.479	11.112	33.356
1478	ASN195	CB	-12.076	9.054	33.736
1479	ASN195	CG	-13.582	9.104	34.008
1480	ASN195	OD1	-14.272	8.076	33.958
1481	ASN195	ND2	-14.076	10.3	34.287
1482	TYR196	N	-9.64	9.613	31.673
1483	TYR196	CA	-8.236	9.692	31.267
1484	TYR196	C	-7.88	11.104	30.817
1485	TYR196	O	-6.953	11.707	31.371
1486	TYR196	CB	-8.065	8.757	30.078
1487	TYR196	CG	-7.054	7.633	30.253
1488	TYR196	CD1	-5.806	7.739	29.658
1489	TYR196	CD2	-7.39	6.5	30.982
1490	TYR196	CE1	-4.884	6.711	29.799
1491	TYR196	CE2	-6.466	5.472	31.126
1492	TYR196	CZ	-5.216	5.581	30.532
1493	TYR196	OH	-4.301	4.56	30.661
1494	LEU197	N	-8.76	11.708	30.032
1495	LEU197	CA	-8.543	13.084	29.57
1496	LEU197	C	-8.718	14.131	30.663
1497	LEU197	O	-7.966	15.11	30.658
1498	LEU197	CB	-9.53	13.394	28.458
1499	LEU197	CG	-9.196	12.63	27.188
1500	LEU197	CD1	-10.305	12.816	26.168
1501	LEU197	CD2	-7.852	13.072	26.619
1502	ASP198	N	-9.49	13.83	31.695
1503	ASP198	CA	-9.6	14.749	32.834
1504	ASP198	C	-8.257	14.841	33.551
1505	ASP198	O	-7.698	15.938	33.694
1506	ASP198	CB	-10.627	14.209	33.829
1507	ASP198	CG	-12.016	14.052	33.214
1508	ASP198	OD1	-12.428	14.949	32.492
1509	ASP198	OD2	-12.706	13.123	33.627
1510	GLU199	N	-7.629	13.685	33.696

1511	GLU199	CA	-6.334	13.598	34.368
1512	GLU199	C	-5.221	14.182	33.506
1513	GLU199	O	-4.521	15.091	33.965
1514	GLU199	CB	-6.053	12.121	34.608
1515	GLU199	CG	-7.157	11.486	35.444
1516	GLU199	CD	-7.084	9.966	35.341
1517	GLU199	OE1	-7.502	9.312	36.287
1518	GLU199	OE2	-6.717	9.484	34.277
1519	LEU200	N	-5.26	13.885	32.219
1520	LEU200	CA	-4.209	14.315	31.289
1521	LEU200	C	-4.22	15.821	31.02
1522	LEU200	O	-3.168	16.467	31.128
1523	LEU200	CB	-4.459	13.57	29.982
1524	LEU200	CG	-3.421	13.888	28.914
1525	LEU200	CD1	-2.036	13.415	29.338
1526	LEU200	CD2	-3.815	13.251	27.587
1527	VAL201	N	-5.406	16.402	30.938
1528	VAL201	CA	-5.521	17.832	30.642
1529	VAL201	C	-5.196	18.69	31.859
1530	VAL201	O	-4.491	19.7	31.709
1531	VAL201	CB	-6.945	18.094	30.153
1532	VAL201	CG1	-7.324	19.57	30.184
1533	VAL201	CG2	-7.159	17.508	28.761
1534	THR202	N	-5.431	18.149	33.045
1535	THR202	CA	-5.103	18.884	34.267
1536	THR202	C	-3.643	18.677	34.654
1537	THR202	O	-2.981	19.624	35.101
1538	THR202	CB	-6.02	18.391	35.378
1539	THR202	OG1	-7.359	18.589	34.945
1540	THR202	CG2	-5.814	19.173	36.671
1541	LYS203	N	-3.08	17.579	34.182
1542	LYS203	CA	-1.672	17.284	34.434
1543	LYS203	C	-0.755	18.113	33.539
1544	LYS203	O	0.305	18.539	34.015
1545	LYS203	CB	-1.474	15.79	34.209
1546	LYS203	CG	-0.041	15.331	34.439
1547	LYS203	CD	0.025	13.812	34.569
1548	LYS203	CE	-0.557	13.099	33.352
1549	LYS203	NZ	0.265	13.325	32.154
1550	LYS204	N	-1.256	18.545	32.391
1551	LYS204	CA	-0.505	19.493	31.553
1552	LYS204	C	-0.788	20.954	31.896
1553	LYS204	O	-0.031	21.846	31.499
1554	LYS204	CB	-0.821	19.218	30.092
1555	LYS204	CG	-0.076	17.965	29.664
1556	LYS204	CD	1.425	18.213	29.729
1557	LYS204	CE	2.202	16.906	29.69
1558	LYS204	NZ	1.918	16.115	30.896
1559	GLU205	N	-1.781	21.179	32.741
1560	GLU205	CA	-2.033	22.524	33.264
1561	GLU205	C	-1.215	22.777	34.526
1562	GLU205	O	-1.027	23.931	34.927
1563	GLU205	CB	-3.518	22.66	33.57
1564	GLU205	CG	-4.309	22.726	32.273

1565	GLU205	CD	-5.788	22.444	32.51
1566	GLU205	OE1	-6.547	22.661	31.573
1567	GLU205	OE2	-6.093	21.798	33.504
1568	ALA206	N	-0.712	21.707	35.12
1569	ALA206	CA	0.208	21.844	36.249
1570	ALA206	C	1.649	21.772	35.756
1571	ALA206	O	2.464	22.661	36.034
1572	ALA206	CB	-0.059	20.711	37.233
1573	ASN207	N	1.92	20.765	34.945
1574	ASN207	CA	3.253	20.587	34.366
1575	ASN207	C	3.307	21.204	32.976
1576	ASN207	O	2.922	20.574	31.982
1577	ASN207	CB	3.568	19.096	34.27
1578	ASN207	CG	3.565	18.441	35.65
1579	ASN207	OD1	4.361	18.793	36.527
1580	ASN207	ND2	2.641	17.515	35.835
1581	ALA208	N	3.786	22.435	32.932
1582	ALA208	CA	3.924	23.166	31.668
1583	ALA208	C	5.045	22.601	30.795
1584	ALA208	O	6.235	22.809	31.052
1585	ALA208	CB	4.202	24.631	31.982
1586	THR209	N	4.636	21.874	29.77
1587	THR209	CA	5.581	21.251	28.834
1588	THR209	C	5.499	21.873	27.446
1589	THR209	O	4.665	22.737	27.168
1590	THR209	CB	5.253	19.774	28.706
1591	THR209	OG1	3.938	19.693	28.18
1592	THR209	CG2	5.296	19.059	30.052
1593	GLU210	N	6.34	21.363	26.562
1594	GLU210	CA	6.411	21.861	25.18
1595	GLU210	C	5.542	21.076	24.19
1596	GLU210	O	5.586	21.361	22.989
1597	GLU210	CB	7.861	21.818	24.692
1598	GLU210	CG	8.791	22.752	25.467
1599	GLU210	CD	9.689	21.967	26.424
1600	GLU210	OE1	9.258	20.906	26.861
1601	GLU210	OE2	10.778	22.442	26.707
1602	ASP211	N	4.786	20.097	24.662
1603	ASP211	CA	3.977	19.273	23.746
1604	ASP211	C	2.732	20.003	23.249
1605	ASP211	O	2.331	21.027	23.817
1606	ASP211	CB	3.605	17.956	24.418
1607	ASP211	CG	2.942	18.154	25.781
1608	ASP211	OD1	2.12	19.054	25.925
1609	ASP211	OD2	3.336	17.427	26.681
1610	ASP212	N	2.034	19.382	22.309
1611	ASP212	CA	0.906	20.044	21.64
1612	ASP212	C	-0.365	20.067	22.496
1613	ASP212	O	-1.223	20.928	22.262
1614	ASP212	CB	0.653	19.331	20.312
1615	ASP212	CG	-0.355	20.078	19.435
1616	ASP212	OD1	-0.505	21.277	19.623
1617	ASP212	OD2	-1.022	19.415	18.653
1618	LEU213	N	-0.398	19.318	23.589

1619	LEU213	CA	-1.529	19.451	24.508
1620	LEU213	C	-1.474	20.819	25.18
1621	LEU213	O	-2.372	21.628	24.907
1622	LEU213	CB	-1.498	18.346	25.557
1623	LEU213	CG	-2.75	18.365	26.427
1624	LEU213	CD1	-4.011	18.334	25.574
1625	LEU213	CD2	-2.751	17.202	27.41
1626	LEU214	N	-0.306	21.193	25.691
1627	LEU214	CA	-0.187	22.52	26.307
1628	LEU214	C	-0.094	23.607	25.241
1629	LEU214	O	-0.613	24.711	25.445
1630	LEU214	CB	1.034	22.608	27.21
1631	LEU214	CG	0.987	23.94	27.954
1632	LEU214	CD1	-0.18	23.972	28.934
1633	LEU214	CD2	2.288	24.25	28.671
1634	GLY215	N	0.35	23.222	24.056
1635	GLY215	CA	0.292	24.093	22.882
1636	GLY215	C	-1.121	24.618	22.629
1637	GLY215	O	-1.327	25.838	22.586
1638	ARG216	N	-2.103	23.733	22.582
1639	ARG216	CA	-3.473	24.198	22.351
1640	ARG216	C	-4.154	24.727	23.616
1641	ARG216	O	-5.077	25.542	23.506
1642	ARG216	CB	-4.3	23.068	21.765
1643	ARG216	CG	-3.636	22.456	20.539
1644	ARG216	CD	-4.555	21.415	19.912
1645	ARG216	NE	-5.402	20.812	20.953
1646	ARG216	CZ	-5.073	19.756	21.699
1647	ARG216	NH1	-3.937	19.093	21.471
1648	ARG216	NH2	-5.905	19.342	22.652
1649	GLN217	N	-3.583	24.445	24.776
1650	GLN217	CA	-4.102	25.002	26.031
1651	GLN217	C	-3.624	26.435	26.28
1652	GLN217	O	-4.198	27.131	27.125
1653	GLN217	CB	-3.648	24.109	27.181
1654	GLN217	CG	-4.235	22.711	27.043
1655	GLN217	CD	-3.691	21.772	28.114
1656	GLN217	OE1	-2.544	21.311	28.052
1657	GLN217	NE2	-4.552	21.446	29.059
1658	ILE218	N	-2.608	26.875	25.551
1659	ILE218	CA	-2.179	28.276	25.625
1660	ILE218	C	-2.638	29.086	24.409
1661	ILE218	O	-2.242	30.25	24.267
1662	ILE218	CB	-0.66	28.352	25.774
1663	ILE218	CG1	0.061	27.755	24.572
1664	ILE218	CG2	-0.211	27.665	27.059
1665	ILE218	CD1	1.574	27.781	24.754
1666	LEU219	N	-3.431	28.478	23.538
1667	LEU219	CA	-3.953	29.194	22.365
1668	LEU219	C	-4.858	30.352	22.75
1669	LEU219	O	-5.716	30.229	23.629
1670	LEU219	CB	-4.756	28.24	21.493
1671	LEU219	CG	-3.859	27.411	20.59
1672	LEU219	CD1	-4.674	26.345	19.873

1673	LEU219	CD2	-3.135	28.304	19.588
1674	LYS220	N	-4.667	31.454	22.047
1675	LYS220	CA	-5.484	32.654	22.234
1676	LYS220	C	-5.341	33.562	21.012
1677	LYS220	O	-4.556	34.519	21.016
1678	LYS220	CB	-5.01	33.38	23.489
1679	LYS220	CG	-5.91	34.56	23.842
1680	LYS220	CD	-5.389	35.289	25.074
1681	LYS220	CE	-6.258	36.494	25.418
1682	LYS220	NZ	-5.74	37.191	26.607
1683	GLN221	N	-6.048	33.217	19.951
1684	GLN221	CA	-5.987	34.031	18.732
1685	GLN221	C	-6.904	35.234	18.892
1686	GLN221	O	-7.981	35.112	19.48
1687	GLN221	CB	-6.389	33.179	17.535
1688	GLN221	CG	-5.417	32.015	17.369
1689	GLN221	CD	-5.828	31.088	16.227
1690	GLN221	OE1	-7.019	30.872	15.966
1691	GLN221	NE2	-4.823	30.508	15.595
1692	ARG222	N	-6.553	36.345	18.268
1693	ARG222	CA	-7.309	37.589	18.486
1694	ARG222	C	-8.774	37.467	18.066
1695	ARG222	O	-9.669	37.72	18.877
1696	ARG222	CB	-6.649	38.705	17.685
1697	ARG222	CG	-7.362	40.034	17.911
1698	ARG222	CD	-6.787	41.134	17.026
1699	ARG222	NE	-7.505	42.401	17.232
1700	ARG222	CZ	-8.368	42.909	16.349
1701	ARG222	NH1	-8.626	42.255	15.213
1702	ARG222	NH2	-8.98	44.068	16.604
1703	GLU223	N	-9.009	36.864	16.912
1704	GLU223	CA	-10.382	36.702	16.426
1705	GLU223	C	-10.985	35.329	16.735
1706	GLU223	O	-12.083	35.029	16.257
1707	GLU223	CB	-10.395	36.959	14.926
1708	GLU223	CG	-9.977	38.396	14.634
1709	GLU223	CD	-9.946	38.649	13.13
1710	GLU223	OE1	-9.041	39.35	12.701
1711	GLU223	OE2	-10.749	38.047	12.434
1712	SER224	N	-10.28	34.5	17.488
1713	SER224	CA	-10.803	33.162	17.775
1714	SER224	C	-11.036	32.957	19.266
1715	SER224	O	-11.791	32.067	19.67
1716	SER224	CB	-9.789	32.13	17.308
1717	SER224	OG	-9.509	32.374	15.941
1718	GLY225	N	-10.409	33.796	20.069
1719	GLY225	CA	-10.436	33.613	21.517
1720	GLY225	C	-9.539	32.[illegible]	21.884
1721	GLY225	O	-8.577	32.[illegible]	21.174
1722	GLU226	N	-9.863	31.[illegible]7	22.998
1723	GLU226	CA	-9.128	30.613	23.422
1724	GLU226	C	-10.067	29.417	23.535
1725	GLU226	O	-11.22	29.553	23.963
1726	GLU226	CB	-8.424	30.894	24.745

1727	GLU226	CG	-9.368	31.316	25.86
1728	GLU226	CD	-8.548	31.714	27.084
1729	GLU226	OE1	-8.364	30.873	27.952
1730	GLU226	OE2	-8.166	32.875	27.147
1731	ALA227	N	-9.567	28.262	23.127
1732	ALA227	CA	-10.372	27.035	23.163
1733	ALA227	C	-10.725	26.657	24.598
1734	ALA227	O	-9.859	26.603	25.477
1735	ALA227	CB	-9.587	25.904	22.508
1736	ASP228	N	-12.009	26.456	24.833
1737	ASP228	CA	-12.471	26.085	26.175
1738	ASP228	C	-12.163	24.618	26.455
1739	ASP228	O	-11.944	23.836	25.52
1740	ASP228	CB	-13.961	26.399	26.323
1741	ASP228	CG	-14.816	25.698	25.268
1742	ASP228	OD1	-14.745	24.475	25.201
1743	ASP228	OD2	-15.656	26.364	24.686
1744	HIS229	N	-12.329	24.215	27.704
1745	HIS229	CA	-11.958	22.854	28.129
1746	HIS229	C	-12.84	21.733	27.559
1747	HIS229	O	-12.334	20.622	27.37
1748	HIS229	CB	-11.971	22.807	29.658
1749	HIS229	CG	-13.265	23.255	30.319
1750	HIS229	ND1	-14.34	22.487	30.584
1751	HIS229	CD2	-13.557	24.519	30.78
1752	HIS229	CE1	-15.293	23.238	31.171
1753	HIS229	NE2	-14.808	24.494	31.292
1754	GLY230	N	-14.024	22.066	27.068
1755	GLY230	CA	-14.88	21.073	26.412
1756	GLY230	C	-14.27	20.684	25.07
1757	GLY230	O	-13.958	19.508	24.84
1758	GLU231	N	-13.866	21.704	24.329
1759	GLU231	CA	-13.239	21.508	23.021
1760	GLU231	C	-11.809	21.001	23.152
1761	GLU231	O	-11.365	20.21	22.315
1762	GLU231	CB	-13.196	22.856	22.318
1763	GLU231	CG	-14.589	23.417	22.086
1764	GLU231	CD	-14.471	24.888	21.707
1765	GLU231	OE1	-15.12	25.296	20.756
1766	GLU231	OE2	-13.758	25.592	22.418
1767	LEU232	N	-11.181	21.28	24.281
1768	LEU232	CA	-9.822	20.803	24.524
1769	LEU232	C	-9.841	19.292	24.755
1770	LEU232	O	-9.061	18.578	24.112
1771	LEU232	CB	-9.297	21.541	25.756
1772	LEU232	CG	-7.777	21.685	25.784
1773	LEU232	CD1	-7.057	20.385	26.124
1774	LEU232	CD2	-7.256	22.293	24.486
1775	VAL233	N	-10.877	18.804	25.419
1776	VAL233	CA	-11.016	17.36	25.627
1777	VAL233	C	-11.406	16.646	24.331
1778	VAL233	O	-10.729	15.676	23.963
1779	VAL233	CB	-12.066	17.13	26.71
1780	VAL233	CG1	-12.478	15.667	26.802

1781	VAL233	CG2	-11.571	17.632	28.062
1782	GLY234	N	-12.258	17.278	23.536
1783	GLY234	CA	-12.641	16.729	22.227
1784	GLY234	C	-11.443	16.59	21.287
1785	GLY234	O	-11.116	15.477	20.849
1786	LEU235	N	-10.687	17.668	21.146
1787	LEU235	CA	-9.532	17.691	20.238
1788	LEU235	C	-8.375	16.809	20.702
1789	LEU235	O	-7.846	16.046	19.882
1790	LEU235	CB	-9.04	19.13	20.146
1791	LEU235	CG	-10.08	20.034	19.495
1792	LEU235	CD1	-9.781	21.505	19.761
1793	LEU235	CD2	-10.2	19.75	18.003
1794	ALA236	N	-8.162	16.713	22.006
1795	ALA236	CA	-7.065	15.885	22.523
1796	ALA236	C	-7.38	14.407	22.375
1797	ALA236	O	-6.525	13.633	21.922
1798	ALA236	CB	-6.861	16.193	24.002
1799	PHE237	N	-8.66	14.095	22.475
1800	PHE237	CA	-9.11	12.723	22.306
1801	PHE237	C	-8.956	12.273	20.864
1802	PHE237	O	-8.27	11.274	20.617
1803	PHE237	CB	-10.58	12.657	22.682
1804	PHE237	CG	-11.12	11.24	22.674
1805	PHE237	CD1	-10.824	10.394	23.733
1806	PHE237	CD2	-11.885	10.786	21.608
1807	PHE237	CE1	-11.305	9.095	23.736
1808	PHE237	CE2	-12.366	9.486	21.61
1809	PHE237	CZ	-12.076	8.644	22.676
1810	LEU238	N	-9.329	13.135	19.931
1811	LEU238	CA	-9.272	12.754	18.516
1812	LEU238	C	-7.845	12.681	17.984
1813	LEU238	O	-7.532	11.745	17.236
1814	LEU238	CB	-10.056	13.766	17.695
1815	LEU238	CG	-11.539	13.75	18.042
1816	LEU238	CD1	-12.279	14.795	17.221
1817	LEU238	CD2	-12.145	12.369	17.814
1818	LEU239	N	-6.947	13.467	18.554
1819	LEU239	CA	-5.551	13.397	18.122
1820	LEU239	C	-4.861	12.158	18.68
1821	LEU239	O	-4.202	11.444	17.913
1822	LEU239	CB	-4.821	14.652	18.586
1823	LEU239	CG	-5.364	15.898	17.894
1824	LEU239	CD1	-4.722	17.162	18.454
1825	LEU239	CD2	-5.169	15.82	16.384
1826	LEU240	N	-5.275	11.736	19.864
1827	LEU240	CA	-4.667	10.56	20.485
1828	LEU240	C	-5.217	9.265	19.877
1829	LEU240	O	-4.445	8.316	19.674
1830	LEU240	CB	-4.952	10.634	21.981
1831	LEU240	CG	-3.966	9.808	22.798
1832	LEU240	CD1	-2.53	10.2	22.479
1833	LEU240	CD2	-4.227	9.976	24.289
1834	ILE241	N	-6.425	9.337	19.333

1835	ILE241	CA	-7.027	8.197	18.621
1836	ILE241	C	-6.509	8.091	17.184
1837	ILE241	O	-6.406	6.98	16.64
1838	ILE241	CB	-8.544	8.391	18.599
1839	ILE241	CG1	-9.122	8.403	20.008
1840	ILE241	CG2	-9.233	7.311	17.771
1841	ILE241	CD1	-8.939	7.06	20.699
1842	ALA242	N	-5.959	9.182	16.676
1843	ALA242	CA	-5.353	9.154	15.345
1844	ALA242	C	-4.049	8.363	15.361
1845	ALA242	O	-3.842	7.511	14.487
1846	ALA242	CB	-5.09	10.583	14.884
1847	GLY243	N	-3.34	8.426	16.473
1848	GLY243	CA	-2.135	7.612	16.614
1849	GLY243	C	-2.461	6.175	17.012
1850	GLY243	O	-2.095	5.238	16.289
1851	HIS244	N	-3.274	6.021	18.047
1852	HIS244	CA	-3.556	4.687	18.603
1853	HIS244	C	-4.424	3.78	17.729
1854	HIS244	O	-4.288	2.555	17.808
1855	HIS244	CB	-4.271	4.846	19.946
1856	HIS244	CG	-3.394	5.206	21.132
1857	HIS244	ND1	-2.995	6.436	21.502
1858	HIS244	CD2	-2.87	4.327	22.051
1859	HIS244	CE1	-2.232	6.348	22.61
1860	HIS244	NE2	-2.156	5.042	22.95
1861	GLU245	N	-5.298	4.33	16.905
1862	GLU245	CA	-6.157	3.454	16.101
1863	GLU245	C	-6.041	3.723	14.61
1864	GLU245	O	-5.883	2.788	13.812
1865	GLU245	CB	-7.616	3.66	16.504
1866	GLU245	CG	-7.895	3.313	17.963
1867	GLU245	CD	-7.613	1.839	18.255
1868	GLU245	OE1	-7.721	1.028	17.348
1869	GLU245	OE2	-7.228	1.562	19.381
1870	THR246	N	-5.987	4.996	14.26
1871	THR246	CA	-6.101	5.374	12.849
1872	THR246	C	-4.863	4.962	12.066
1873	THR246	O	-4.949	4.04	11.244
1874	THR246	CB	-6.314	6.88	12.759
1875	THR246	OG1	-7.415	7.225	13.59
1876	THR246	CG2	-6.614	7.344	11.338
1877	THR247	N	-3.702	5.384	12.532
1878	THR247	CA	-2.48	5.072	11.792
1879	THR247	C	-2.013	3.634	12.044
1880	THR247	O	-1.437	3.032	11.132
1881	THR247	CB	-1.4	6.078	12.171
1882	THR247	OG1	-1.937	7.39	12.062
1883	THR247	CG2	-0.192	5.981	11.246
1884	ALA248	N	-2.533	3.007	13.09
1885	ALA248	CA	-2.225	1.596	13.35
1886	ALA248	C	-2.915	0.676	12.342
1887	ALA248	O	-2.236	-0.089	11.643
1888	ALA248	CB	-2.678	1.25	14.763

1889	ASN249	N	-4.175	0.958	12.049
1890	ASN249	CA	-4.878	0.157	11.042
1891	ASN249	C	-4.453	0.517	9.624
1892	ASN249	O	-4.313	-0.39	8.791
1893	ASN249	CB	-6.377	0.361	11.199
1894	ASN249	CG	-6.902	-0.561	12.291
1895	ASN249	OD1	-6.261	-1.569	12.613
1896	ASN249	ND2	-8.133	-0.32	12.703
1897	MET250	N	-3.945	1.727	9.463
1898	MET250	CA	-3.472	2.183	8.159
1899	MET250	C	-2.137	1.529	7.787
1900	MET250	O	-2.018	1.009	6.669
1901	MET250	CB	-3.231	3.702	8.255
1902	MET250	CG	-3.343	4.33	6.851
1903	MET250	SD	-2.234	5.768	6.665
1904	MET250	CE	-1.954	6.241	8.406
1905	ILE251	N	-1.267	1.317	8.764
1906	ILE251	CA	0.019	0.667	8.477
1907	ILE251	C	-0.132	-0.844	8.328
1908	ILE251	O	0.449	-1.427	7.402
1909	ILE251	CB	1.001	0.949	9.613
1910	ILE251	CG1	1.293	2.434	9.757
1911	ILE251	CG2	2.305	0.188	9.404
1912	ILE251	CD1	2.264	2.698	10.902
1913	SER252	N	-1.081	-1.421	9.047
1914	SER252	CA	-1.254	-2.875	8.973
1915	SER252	C	-1.947	-3.301	7.679
1916	SER252	O	-1.444	-4.204	6.998
1917	SER252	CB	-2.03	-3.36	10.197
1918	SER252	OG	-3.28	-2.684	10.279
1919	LEU253	N	-2.85	-2.465	7.194
1920	LEU253	CA	-3.558	-2.762	5.948
1921	LEU253	C	-2.699	-2.386	4.739
1922	LEU253	O	-2.665	-3.129	3.748
1923	LEU253	CB	-4.857	-1.963	5.994
1924	LEU253	CG	-5.781	-2.185	4.804
1925	LEU253	CD1	-6.009	-3.665	4.521
1926	LEU253	CD2	-7.109	-1.479	5.058
1927	GLY254	N	-1.818	-1.42	4.948
1928	GLY254	CA	-0.841	-1.031	3.933
1929	GLY254	C	0.161	-2.148	3.671
1930	GLY254	O	0.267	-2.62	2.531
1931	THR255	N	0.707	-2.706	4.742
1932	THR255	CA	1.711	-3.772	4.62
1933	THR255	C	1.123	-5.042	4.017
1934	THR255	O	1.715	-5.592	3.079
1935	THR255	CB	2.255	-4.105	6.007
1936	THR255	OG1	2.837	-2.935	6.563
1937	THR255	CG2	3.334	-5.18	5.938
1938	VAL256	N	-0.133	-5.321	4.331
1939	VAL256	CA	-0.797	-6.505	3.781
1940	VAL256	C	-1.11	-6.37	2.291
1941	VAL256	O	-0.832	-7.307	1.531
1942	VAL256	CB	-2.083	-6.706	4.571

1943	VAL256	CG1	-3.028	-7.693	3.905
1944	VAL256	CG2	-1.774	-7.144	5.993
1945	THR257	N	-1.372	-5.158	1.833
1946	THR257	CA	-1.675	-4.982	0.413
1947	THR257	C	-0.401	-4.902	-0.427
1948	THR257	O	-0.357	-5.499	-1.512
1949	THR257	CB	-2.502	-3.717	0.248
1950	THR257	OG1	-3.63	-3.818	1.106
1951	THR257	CG2	-3.002	-3.558	-1.183
1952	LEU258	N	0.69	-4.465	0.185
1953	LEU258	CA	1.976	-4.434	-0.526
1954	LEU258	C	2.588	-5.828	-0.61
1955	LEU258	O	3.147	-6.205	-1.648
1956	LEU258	CB	2.936	-3.524	0.233
1957	LEU258	CG	2.45	-2.08	0.263
1958	LEU258	CD1	3.329	-1.229	1.172
1959	LEU258	CD2	2.391	-1.492	-1.141
1960	LEU259	N	2.248	-6.652	0.368
1961	LEU259	CA	2.721	-8.034	0.407
1962	LEU259	C	1.818	-8.965	-0.407
1963	LEU259	O	2.223	-10.083	-0.747
1964	LEU259	CB	2.742	-8.462	1.869
1965	LEU259	CG	3.979	-9.291	2.183
1966	LEU259	CD1	5.235	-8.559	1.727
1967	LEU259	CD2	4.05	-9.61	3.672
1968	GLU260	N	0.649	-8.473	-0.791
1969	GLU260	CA	-0.221	-9.215	-1.707
1970	GLU260	C	0.163	-8.932	-3.151
1971	GLU260	O	0.033	-9.804	-4.019
1972	GLU260	CB	-1.67	-8.773	-1.531
1973	GLU260	CG	-2.53	-9.85	-0.883
1974	GLU260	CD	-2.442	-9.78	0.637
1975	GLU260	OE1	-1.632	-10.498	1.204
1976	GLU260	OE2	-3.287	-9.103	1.202
1977	ASN261	N	0.693	-7.743	-3.382
1978	ASN261	CA	1.158	-7.381	-4.723
1979	ASN261	C	2.669	-7.181	-4.742
1980	ASN261	O	3.134	-6.032	-4.804
1981	ASN261	CB	0.468	-6.089	-5.161
1982	ASN261	CG	-0.986	-6.311	-5.586
1983	ASN261	OD1	-1.784	-6.942	-4.881
1984	ASN261	ND2	-1.339	-5.701	-6.705
1985	PRO262	N	3.404	-8.259	-4.986
1986	PRO262	CA	4.864	-8.219	-4.846
1987	PRO262	C	5.563	-7.432	-5.958
1988	PRO262	O	6.612	-6.834	-5.706
1989	PRO262	CB	5.298	-9.652	-4.871
1990	PRO262	CG	4.108	-10.533	-5.223
1991	PRO262	CD	2.912	-9.601	-5.319
1992	ASP263	N	4.884	-7.222	-7.077
1993	ASP263	CA	5.442	-6.411	-8.166
1994	ASP263	C	5.27	-4.909	-7.918
1995	ASP263	O	6.133	-4.124	-8.327
1996	ASP263	CB	4.783	-6.822	-9.488

1997	ASP263	CG	3.253	-6.778	-9.42
1998	ASP263	OD1	2.69	-5.734	-9.721
1999	ASP263	OD2	2.673	-7.766	-8.992
2000	GLN264	N	4.358	-4.558	-7.024
2001	GLN264	CA	4.149	-3.154	-6.675
2002	GLN264	C	5.104	-2.803	-5.545
2003	GLN264	O	5.782	-1.769	-5.59
2004	GLN264	CB	2.709	-3.002	-6.206
2005	GLN264	CG	1.723	-3.483	-7.265
2006	GLN264	CD	1.637	-2.485	-8.412
2007	GLN264	OE1	1.631	-1.274	-8.178
2008	GLN264	NE2	1.592	-2.991	-9.63
2009	LEU265	N	5.398	-3.825	-4.758
2010	LEU265	CA	6.389	-3.701	-3.693
2011	LEU265	C	7.808	-3.677	-4.263
2012	LEU265	O	8.639	-2.888	-3.798
2013	LEU265	CB	6.218	-4.903	-2.775
2014	LEU265	CG	7.134	-4.809	-1.565
2015	LEU265	CD1	6.869	-3.518	-0.802
2016	LEU265	CD2	6.958	-6.023	-0.662
2017	ALA266	N	7.993	-4.309	-5.411
2018	ALA266	CA	9.286	-4.267	-6.093
2019	ALA266	C	9.528	-2.929	-6.785
2020	ALA266	O	10.66	-2.434	-6.737
2021	ALA266	CB	9.333	-5.39	-7.123
2022	LYS267	N	8.466	-2.235	-7.167
2023	LYS267	CA	8.641	-0.891	-7.725
2024	LYS267	C	8.887	0.136	-6.625
2025	LYS267	O	9.706	1.042	-6.818
2026	LYS267	CB	7.406	-0.501	-8.523
2027	LYS267	CG	7.223	-1.394	-9.742
2028	LYS267	CD	6.072	-0.894	-10.604
2029	LYS267	CE	4.779	-0.825	-9.803
2030	LYS267	NZ	3.688	-0.267	-10.615
2031	ILE268	N	8.413	-0.162	-5.427
2032	ILE268	CA	8.717	0.664	-4.254
2033	ILE268	C	10.181	0.531	-3.84
2034	ILE268	O	10.879	1.544	-3.697
2035	ILE268	CB	7.827	0.171	-3.117
2036	ILE268	CG1	6.38	0.576	-3.335
2037	ILE268	CG2	8.311	0.638	-1.75
2038	ILE268	CD1	5.504	0.057	-2.205
2039	LYS269	N	10.693	-0.688	-3.902
2040	LYS269	CA	12.068	-0.95	-3.463
2041	LYS269	C	13.116	-0.675	-4.542
2042	LYS269	O	14.306	-0.554	-4.228
2043	LYS269	CB	12.126	-2.405	-3.021
2044	LYS269	CG	11.167	-2.628	-1.858
2045	LYS269	CD	10.997	-4.107	-1.542
2046	LYS269	CE	12.315	-4.756	-1.148
2047	LYS269	NZ	12.106	-6.181	-0.856
2048	ALA270	N	12.679	-0.53	-5.782
2049	ALA270	CA	13.585	-0.106	-6.851
2050	ALA270	C	13.478	1.396	-7.101

2051	ALA270	O	14.286	1.974	-7.838
2052	ALA270	CB	13.233	-0.863	-8.125
2053	ASP271	N	12.486	2.017	-6.486
2054	ASP271	CA	12.271	3.453	-6.649
2055	ASP271	C	11.505	4.006	-5.448
2056	ASP271	O	10.267	4.02	-5.445
2057	ASP271	CB	11.48	3.653	-7.944
2058	ASP271	CG	11.354	5.125	-8.337
2059	ASP271	OD1	10.975	5.919	-7.482
2060	ASP271	OD2	11.493	5.405	-9.517
2061	PRO272	N	12.238	4.705	-4.592
2062	PRO272	CA	11.686	5.248	-3.337
2063	PRO272	C	10.72	6.438	-3.497
2064	PRO272	O	9.973	6.74	-2.558
2065	PRO272	CB	12.887	5.657	-2.54
2066	PRO272	CG	14.133	5.544	-3.406
2067	PRO272	CD	13.673	4.968	-4.734
2068	GLY273	N	10.586	6.971	-4.702
2069	GLY273	CA	9.607	8.03	-4.968
2070	GLY273	C	8.207	7.423	-5.037
2071	GLY273	O	7.257	7.968	-4.456
2072	LYS274	N	8.167	6.171	-5.473
2073	LYS274	CA	6.916	5.418	-5.566
2074	LYS274	C	6.39	4.954	-4.21
2075	LYS274	O	5.225	4.55	-4.144
2076	LYS274	CB	7.138	4.184	-6.431
2077	LYS274	CG	7.528	4.547	-7.856
2078	LYS274	CD	7.755	3.287	-8.681
2079	LYS274	CE	8.177	3.615	-10.107
2080	LYS274	NZ	8.465	2.383	-10.858
2081	THR275	N	7.12	5.182	-3.127
2082	THR275	CA	6.593	4.814	-1.813
2083	THR275	C	5.522	5.804	-1.352
2084	THR275	O	4.516	5.354	-0.798
2085	THR275	CB	7.725	4.76	-0.789
2086	THR275	OG1	8.169	6.074	-0.485
2087	THR275	CG2	8.912	3.963	-1.305
2088	LEU276	N	5.564	7.036	-1.844
2089	LEU276	CA	4.543	8.012	-1.446
2090	LEU276	C	3.312	7.905	-2.346
2091	LEU276	O	2.175	8.051	-1.876
2092	LEU276	CB	5.14	9.411	-1.538
2093	LEU276	CG	4.182	10.462	-0.987
2094	LEU276	CD1	3.836	10.177	0.472
2095	LEU276	CD2	4.77	11.861	-1.133
2096	ALA277	N	3.53	7.375	-3.539
2097	ALA277	CA	2.417	7.126	-4.451
2098	ALA277	C	1.711	5.836	-4.052
2099	ALA277	O	0.475	5.796	-4.026
2100	ALA277	CB	2.963	7.021	-5.869
2101	ALA278	N	2.472	4.947	-3.431
2102	ALA278	CA	1.909	3.727	-2.859
2103	ALA278	C	1.12	4.01	-1.591
2104	ALA278	O	0.051	3.416	-1.427

2105	ALA278	CB	3.048	2.773	-2.523
2106	ILE279	N	1.472	5.064	-0.867
2107	ILE279	CA	0.698	5.447	0.324
2108	ILE279	C	-0.692	5.926	-0.078
2109	ILE279	O	-1.691	5.368	0.396
2110	ILE279	CB	1.401	6.588	1.063
2111	ILE279	CG1	2.806	6.209	1.513
2112	ILE279	CG2	0.577	7.041	2.264
2113	ILE279	CD1	2.805	4.984	2.416
2114	GLU280	N	-0.748	6.688	-1.159
2115	GLU280	CA	-2.037	7.217	-1.616
2116	GLU280	C	-2.849	6.159	-2.358
2117	GLU280	O	-4.075	6.123	-2.217
2118	GLU280	CB	-1.784	8.404	-2.537
2119	GLU280	CG	-0.943	9.484	-1.862
2120	GLU280	CD	-1.616	9.992	-0.587
2121	GLU280	OE1	-2.453	10.875	-0.699
2122	GLU280	OE2	-1.19	9.569	0.479
2123	GLU281	N	-2.169	5.173	-2.916
2124	GLU281	CA	-2.857	4.083	-3.604
2125	GLU281	C	-3.402	3.048	-2.616
2126	GLU281	O	-4.497	2.514	-2.842
2127	GLU281	CB	-1.846	3.441	-4.546
2128	GLU281	CG	-2.451	2.329	-5.39
2129	GLU281	CD	-3.395	2.862	-6.465
2130	GLU281	OE1	-3.893	2.017	-7.199
2131	GLU281	OE2	-3.446	4.068	-6.653
2132	LEU282	N	-2.776	2.957	-1.452
2133	LEU282	CA	-3.272	2.102	-0.369
2134	LEU282	C	-4.527	2.703	0.232
2135	LEU282	O	-5.563	2.03	0.269
2136	LEU282	CB	-2.212	2.019	0.727
2137	LEU282	CG	-1.025	1.151	0.332
2138	LEU282	CD1	0.163	1.385	1.256
2139	LEU282	CD2	-1.415	-0.319	0.305
2140	LEU283	N	-4.511	4.018	0.378
2141	LEU283	CA	-5.666	4.738	0.922
2142	LEU283	C	-6.823	4.808	-0.066
2143	LEU283	O	-7.989	4.766	0.346
2144	LEU283	CB	-5.202	6.145	1.257
2145	LEU283	CG	-4.178	6.103	2.379
2146	LEU283	CD1	-3.386	7.399	2.461
2147	LEU283	CD2	-4.848	5.766	3.706
2148	ARG284	N	-6.512	4.723	-1.346
2149	ARG284	CA	-7.561	4.67	-2.355
2150	ARG284	C	-8.306	3.337	-2.3
2151	ARG284	O	-9.482	3.316	-1.923
2152	ARG284	CB	-6.921	4.824	-3.726
2153	ARG284	CG	-7.99	4.956	-4.798
2154	ARG284	CD	-7.417	4.674	-6.18
2155	ARG284	NE	-6.879	3.305	-6.258
2156	ARG284	CZ	-7.603	2.231	-6.583
2157	ARG284	NH1	-8.911	2.35	-6.816
2158	ARG284	NH2	-7.021	1.032	-6.658

2159	ILE285	N	-7.588	2.233	-2.423
2160	ILE285	CA	-8.284	0.942	-2.519
2161	ILE285	C	-8.742	0.397	-1.155
2162	ILE285	O	-9.703	-0.385	-1.087
2163	ILE285	CB	-7.36	-0.039	-3.247
2164	ILE285	CG1	-8.033	-1.383	-3.499
2165	ILE285	CG2	-6.045	-0.238	-2.501
2166	ILE285	CD1	-7.119	-2.327	-4.272
2167	PHE286	N	-8.188	0.934	-0.082
2168	PHE286	CA	-8.543	0.5	1.268
2169	PHE286	C	-8.451	1.645	2.27
2170	PHE286	O	-7.544	1.66	3.115
2171	PHE286	CB	-7.575	-0.594	1.708
2172	PHE286	CG	-7.737	-1.948	1.025
2173	PHE286	CD1	-6.675	-2.503	0.323
2174	PHE286	CD2	-8.943	-2.632	1.117
2175	PHE286	CE1	-6.822	-3.736	-0.298
2176	PHE286	CE2	-9.09	-3.865	0.495
2177	PHE286	CZ	-8.03	-4.417	-0.213
2178	THR287	N	-9.377	2.584	2.193
2179	THR287	CA	-9.413	3.636	3.212
2180	THR287	C	-9.931	3.053	4.519
2181	THR287	O	-10.843	2.216	4.543
2182	THR287	CB	-10.294	4.801	2.77
2183	THR287	OG1	-10.207	5.833	3.745
2184	THR287	CG2	-11.759	4.423	2.643
2185	ILE288	N	-9.305	3.459	5.609
2186	ILE288	CA	-9.745	2.966	6.911
2187	ILE288	C	-10.966	3.747	7.391
2188	ILE288	O	-11.856	3.155	8.014
2189	ILE288	CB	-8.584	3.044	7.894
2190	ILE288	CG1	-8.04	4.459	8.013
2191	ILE288	CG2	-7.469	2.097	7.461
2192	ILE288	CD1	-6.938	4.507	9.052
2193	ALA289	N	-11.116	4.965	6.89
2194	ALA289	CA	-12.34	5.743	7.09
2195	ALA289	C	-13.315	5.37	5.982
2196	ALA289	O	-13.433	6.062	4.964
2197	ALA289	CB	-12.003	7.228	7.013
2198	GLU290	N	-13.969	4.239	6.174
2199	GLU290	CA	-14.796	3.652	5.128
2200	GLU290	C	-16.223	4.179	5.178
2201	GLU290	O	-16.891	4.234	4.138
2202	GLU290	CB	-14.766	2.14	5.34
2203	GLU290	CG	-15.669	1.375	4.381
2204	GLU290	CD	-15.736	-0.091	4.802
2205	GLU290	OE1	-16.751	-0.475	5.367
2206	GLU290	OE2	-14.809	-0.819	4.472
2207	THR291	N	-16.659	4.619	6.347
2208	THR291	CA	-17.992	5.216	6.481
2209	THR291	C	-17.983	6.47	7.349
2210	THR291	O	-17.68	6.437	8.55
2211	THR291	CB	-18.978	4.219	7.094
2212	THR291	OG1	-18.522	3.832	8.382

2213	THR291	CG2	-19.168	2.961	6.257
2214	ALA292	N	-18.397	7.562	6.734
2215	ALA292	CA	-18.676	8.799	7.471
2216	ALA292	C	-20.103	8.704	8.001
2217	ALA292	O	-21.051	9.169	7.355
2218	ALA292	CB	-18.552	9.986	6.521
2219	THR293	N	-20.231	8.1	9.172
2220	THR293	CA	-21.535	7.709	9.721
2221	THR293	C	-22.161	8.802	10.585
2222	THR293	O	-22.152	8.733	11.82
2223	THR293	CB	-21.308	6.447	10.546
2224	THR293	OG1	-20.564	5.523	9.756
2225	THR293	CG2	-22.617	5.788	10.962
2226	SER294	N	-22.703	9.805	9.913
2227	SER294	CA	-23.293	10.956	10.601
2228	SER294	C	-24.198	11.766	9.675
2229	SER294	O	-25.386	11.443	9.529
2230	SER294	CB	-22.167	11.822	11.164
2231	SER294	OG	-20.976	11.559	10.426
2232	ARG295	N	-23.598	12.789	9.076
2233	ARG295	CA	-24.233	13.782	8.187
2234	ARG295	C	-25.738	13.903	8.366
2235	ARG295	O	-26.524	13.3	7.627
2236	ARG295	CB	-23.905	13.424	6.747
2237	ARG295	CG	-22.4	13.455	6.518
2238	ARG295	CD	-21.819	14.841	6.786
2239	ARG295	NE	-20.362	14.859	6.577
2240	ARG295	CZ	-19.475	14.679	7.56
2241	ARG295	NH1	-19.892	14.437	8.805
2242	ARG295	NH2	-18.167	14.719	7.293
2243	PHE296	N	-26.119	14.646	9.387
2244	PHE296	CA	-27.528	14.825	9.712
2245	PHE296	C	-28.176	15.754	8.701
2246	PHE296	O	-27.736	16.899	8.529
2247	PHE296	CB	-27.623	15.428	11.11
2248	PHE296	CG	-29.052	15.695	11.562
2249	PHE296	CD1	-29.564	16.985	11.533
2250	PHE296	CD2	-29.843	14.643	12.002
2251	PHE296	CE1	-30.871	17.221	11.936
2252	PHE296	CE2	-31.149	14.879	12.406
2253	PHE296	CZ	-31.663	16.167	12.37
2254	ALA297	N	-29.2	15.255	8.032
2255	ALA297	CA	-29.931	16.073	7.065
2256	ALA297	C	-30.783	17.111	7.781
2257	ALA297	O	-31.769	16.781	8.45
2258	ALA297	CB	-30.819	15.165	6.224
2259	THR298	N	-30.369	18.361	7.668
2260	THR298	CA	-31.129	19.47	8.255
2261	THR298	C	-32.139	20.005	7.246
2262	THR298	O	-33.087	20.712	7.603
2263	THR298	CB	-30.17	20.586	8.659
2264	THR298	OG1	-29.565	21.12	7.488
2265	THR298	CG2	-29.068	20.082	9.582
2266	ALA299	N	-31.926	19.649	5.992

2267	ALA299	CA	-32.881	19.968	4.932
2268	ALA299	C	-33.091	18.734	4.068
2269	ALA299	O	-32.427	17.712	4.27
2270	ALA299	CB	-32.331	21.11	4.086
2271	ASP300	N	-34.041	18.817	3.151
2272	ASP300	CA	-34.256	17.727	2.191
2273	ASP300	C	-33.253	17.852	1.048
2274	ASP300	O	-33.498	18.545	0.053
2275	ASP300	CB	-35.679	17.801	1.648
2276	ASP300	CG	-36.682	17.714	2.793
2277	ASP300	OD1	-36.686	16.69	3.463
2278	ASP300	OD2	-37.289	18.733	3.09
2279	VAL301	N	-32.128	17.177	1.199
2280	VAL301	CA	-31.029	17.337	0.244
2281	VAL301	C	-31.065	16.261	-0.833
2282	VAL301	O	-30.956	15.062	-0.55
2283	VAL301	CB	-29.711	17.263	1.007
2284	VAL301	CG1	-28.543	17.673	0.118
2285	VAL301	CG2	-29.756	18.154	2.24
2286	GLU302	N	-31.242	16.695	-2.067
2287	GLU302	CA	-31.23	15.75	-3.184
2288	GLU302	C	-29.799	15.413	-3.603
2289	GLU302	O	-29.141	16.178	-4.318
2290	GLU302	CB	-31.98	16.355	-4.363
2291	GLU302	CG	-32.053	15.344	-5.497
2292	GLU302	CD	-32.662	15.959	-6.75
2293	GLU302	OE1	-33.484	16.852	-6.606
2294	GLU302	OE2	-32.169	15.628	-7.82
2295	ILE303	N	-29.365	14.227	-3.222
2296	ILE303	CA	-28.014	13.766	-3.539
2297	ILE303	C	-28.053	12.812	-4.726
2298	ILE303	O	-28.452	11.647	-4.6
2299	ILE303	CB	-27.438	13.076	-2.307
2300	ILE303	CG1	-27.329	14.056	-1.148
2301	ILE303	CG2	-26.066	12.49	-2.608
2302	ILE303	CD1	-26.305	15.146	-1.441
2303	GLY304	N	-27.715	13.356	-5.885
2304	GLY304	CA	-27.705	12.592	-7.139
2305	GLY304	C	-29.056	11.935	-7.402
2306	GLY304	O	-29.187	10.708	-7.311
2307	GLY305	N	-30.079	12.757	-7.573
2308	GLY305	CA	-31.432	12.229	-7.805
2309	GLY305	C	-32.226	11.982	-6.517
2310	GLY305	O	-33.289	12.584	-6.314
2311	THR306	N	-31.694	11.132	-5.653
2312	THR306	CA	-32.399	10.717	-4.431
2313	THR306	C	-32.569	11.859	-3.43
2314	THR306	O	-31.597	12.497	-3.015
2315	THR306	CB	-31.591	9.598	-3.782
2316	THR306	OG1	-31.461	8.534	-4.716
2317	THR306	CG2	-32.278	9.051	-2.537
2318	LEU307	N	-33.811	12.127	-3.066
2319	LEU307	CA	-34.093	13.162	-2.068
2320	LEU307	C	-33.971	12.6	-0.652

2321	LEU307	O	-34.803	11.799	-0.209
2322	LEU307	CB	-35.513	13.67	-2.295
2323	LEU307	CG	-35.845	14.852	-1.391
2324	LEU307	CD1	-34.946	16.039	-1.71
2325	LEU307	CD2	-37.31	15.248	-1.534
2326	ILE308	N	-32.93	13.021	0.045
2327	ILE308	CA	-32.738	12.616	1.439
2328	ILE308	C	-33.586	13.486	2.362
2329	ILE308	O	-33.481	14.719	2.356
2330	ILE308	CB	-31.253	12.742	1.764
2331	ILE308	CG1	-30.456	11.77	0.901
2332	ILE308	CG2	-30.976	12.507	3.245
2333	ILE308	CD1	-28.974	11.794	1.246
2334	ARG309	N	-34.466	12.834	3.101
2335	ARG309	CA	-35.386	13.543	3.993
2336	ARG309	C	-34.674	14.125	5.209
2337	ARG309	O	-33.807	13.486	5.824
2338	ARG309	CB	-36.447	12.563	4.474
2339	ARG309	CG	-37.117	11.841	3.312
2340	ARG309	CD	-38.079	10.778	3.83
2341	ARG309	NE	-38.721	10.055	2.721
2342	ARG309	CZ	-40.046	9.951	2.594
2343	ARG309	NH1	-40.85	10.528	3.49
2344	ARG309	NH2	-40.566	9.278	1.566
2345	ALA310	N	-35.099	15.325	5.566
2346	ALA310	CA	-34.597	15.999	6.763
2347	ALA310	C	-34.952	15.189	8.003
2348	ALA310	O	-36.005	14.542	8.07
2349	ALA310	CB	-35.223	17.386	6.853
2350	GLY311	N	-34	15.115	8.913
2351	GLY311	CA	-34.172	14.325	10.13
2352	GLY311	C	-33.475	12.968	10.042
2353	GLY311	O	-33.472	12.217	11.023
2354	GLU312	N	-32.982	12.611	8.866
2355	GLU312	CA	-32.294	11.322	8.719
2356	GLU312	C	-30.776	11.471	8.737
2357	GLU312	O	-30.236	12.577	8.599
2358	GLU312	CB	-32.743	10.651	7.429
2359	GLU312	CG	-34.243	10.386	7.453
2360	GLU312	CD	-34.639	9.537	6.252
2361	GLU312	OE1	-34.686	10.083	5.156
2362	GLU312	OE2	-34.723	8.33	6.419
2363	GLY313	N	-30.107	10.356	8.981
2364	GLY313	CA	-28.64	10.335	8.994
2365	GLY313	C	-28.079	9.813	7.673
2366	GLY313	O	-28.674	8.944	7.02
2367	VAL314	N	-26.996	10.429	7.237
2368	VAL314	CA	-26.33	10.028	5.994
2369	VAL314	C	-24.93	9.467	6.267
2370	VAL314	O	-24.127	10.02	7.033
2371	VAL314	CB	-26.28	11.246	5.073
2372	VAL314	CG1	-25.639	10.942	3.724
2373	VAL314	CG2	-27.681	11.804	4.861
2374	VAL315	N	-24.674	8.328	5.649

2375	VAL315	CA	-23.386	7.646	5.773
2376	VAL315	C	-22.647	7.666	4.435
2377	VAL315	O	-23.025	6.975	3.479
2378	VAL315	CB	-23.634	6.207	6.213
2379	VAL315	CG1	-22.325	5.437	6.347
2380	VAL315	CG2	-24.404	6.163	7.528
2381	GLY316	N	-21.6	8.467	4.374
2382	GLY316	CA	-20.789	8.539	3.152
2383	GLY316	C	-19.797	7.382	3.096
2384	GLY316	O	-18.903	7.28	3.946
2385	LEU317	N	-19.978	6.508	2.121
2386	LEU317	CA	-19.102	5.343	1.978
2387	LEU317	C	-17.841	5.722	1.218
2388	LEU317	O	-17.758	5.485	0.009
2389	LEU317	CB	-19.835	4.256	1.199
2390	LEU317	CG	-20.312	3.094	2.064
2391	LEU317	CD1	-19.129	2.374	2.697
2392	LEU317	CD2	-21.328	3.519	3.121
2393	SER318	N	-16.794	6.056	1.951
2394	SER318	CA	-15.563	6.559	1.34
2395	SER318	C	-14.789	5.483	0.588
2396	SER318	O	-14.286	5.777	-0.503
2397	SER318	CB	-14.689	7.158	2.434
2398	SER318	OG	-13.375	7.32	1.915
2399	ASN319	N	-14.954	4.222	0.954
2400	ASN319	CA	-14.267	3.196	0.162
2401	ASN319	C	-15.089	2.774	-1.058
2402	ASN319	O	-14.498	2.343	-2.052
2403	ASN319	CB	-13.899	1.982	1.004
2404	ASN319	CG	-12.531	1.507	0.516
2405	ASN319	OD1	-11.628	2.333	0.321
2406	ASN319	ND2	-12.378	0.209	0.332
2407	ALA320	N	-16.362	3.139	-1.091
2408	ALA320	CA	-17.181	2.889	-2.283
2409	ALA320	C	-17.001	4.055	-3.248
2410	ALA320	O	-16.897	3.856	-4.464
2411	ALA320	CB	-18.642	2.78	-1.875
2412	GLY321	N	-16.68	5.197	-2.666
2413	GLY321	CA	-16.233	6.36	-3.426
2414	GLY321	C	-14.942	6.045	-4.17
2415	GLY321	O	-14.924	6.106	-5.404
2416	ASN322	N	-13.958	5.508	-3.466
2417	ASN322	CA	-12.683	5.172	-4.113
2418	ASN322	C	-12.765	3.924	-5.006
2419	ASN322	O	-11.954	3.769	-5.927
2420	ASN322	CB	-11.651	4.902	-3.035
2421	ASN322	CG	-11.54	6.013	-1.994
2422	ASN322	OD1	-11.701	7.211	-2.278
2423	ASN322	ND2	-11.095	5.595	-0.824
2424	HIS323	N	-13.785	3.103	-4.807
2425	HIS323	CA	-14.068	1.985	-5.716
2426	HIS323	C	-15.037	2.337	-6.846
2427	HIS323	O	-15.541	1.435	-7.525
2428	HIS323	CB	-14.625	0.804	-4.939

2429	HIS323	CG	-13.581	0.008	-4.19
2430	HIS323	ND1	-13.802	-0.807	-3.144
2431	HIS323	CD2	-12.233	-0.04	-4.46
2432	HIS323	CE1	-12.634	-1.351	-2.748
2433	HIS323	NE2	-11.664	-0.875	-3.563
2434	ASP324	N	-15.353	3.608	-7.007
2435	ASP324	CA	-16.209	4.041	-8.109
2436	ASP324	C	-15.409	4.076	-9.411
2437	ASP324	O	-14.628	5.012	-9.642
2438	ASP324	CB	-16.72	5.431	-7.737
2439	ASP324	CG	-17.711	6.002	-8.74
2440	ASP324	OD1	-18.738	6.476	-8.275
2441	ASP324	OD2	-17.28	6.257	-9.859
2442	PRO325	N	-15.831	3.237	-10.349
2443	PRO325	CA	-15.082	2.989	-11.595
2444	PRO325	C	-15.201	4.099	-12.648
2445	PRO325	O	-14.504	4.065	-13.667
2446	PRO325	CB	-15.653	1.713	-12.134
2447	PRO325	CG	-16.9	1.346	-11.345
2448	PRO325	CD	-17.01	2.374	-10.232
2449	ASP326	N	-16.008	5.11	-12.361
2450	ASP326	CA	-16.206	6.248	-13.259
2451	ASP326	C	-15.146	7.312	-12.983
2452	ASP326	O	-14.924	8.216	-13.797
2453	ASP326	CB	-17.597	6.826	-12.994
2454	ASP326	CG	-18.675	5.753	-13.155
2455	ASP326	OD1	-19.125	5.571	-14.277
2456	ASP326	OD2	-18.963	5.068	-12.179
2457	GLY327	N	-14.468	7.162	-11.857
2458	GLY327	CA	-13.318	8.005	-11.542
2459	GLY327	C	-12.061	7.145	-11.594
2460	GLY327	O	-11.166	7.366	-12.418
2461	PHE328	N	-12.046	6.12	-10.76
2462	PHE328	CA	-10.893	5.218	-10.705
2463	PHE328	C	-11.119	4.009	-11.602
2464	PHE328	O	-11.92	3.114	-11.3
2465	PHE328	CB	-10.653	4.81	-9.257
2466	PHE328	CG	-10.261	5.995	-8.376
2467	PHE328	CD1	-9.098	6.702	-8.651
2468	PHE328	CD2	-11.07	6.379	-7.314
2469	PHE328	CE1	-8.737	7.784	-7.858
2470	PHE328	CE2	-10.709	7.459	-6.519
2471	PHE328	CZ	-9.542	8.161	-6.791
2472	GLU329	N	-10.377	4.006	-12.696
2473	GLU329	CA	-10.511	2.993	-13.752
2474	GLU329	C	-10.048	1.63	-13.253
2475	GLU329	O	-8.847	1.399	-13.092
2476	GLU329	CB	-9.673	3.409	-14.962
2477	GLU329	CG	-10.104	4.752	-15.557
2478	GLU329	CD	-9.106	5.864	-15.215
2479	GLU329	OE1	-8.54	5.804	-14.132
2480	GLU329	OE2	-8.904	6.724	-16.059
2481	ASN330	N	-10.987	0.698	-13.249
2482	ASN330	CA	-10.826	-0.597	-12.566

2483	ASN330	C	-10.252	-0.375	-11.171
2484	ASN330	O	-9.065	-0.629	-10.929
2485	ASN330	CB	-9.925	-1.547	-13.355
2486	ASN330	CG	-9.943	-2.959	-12.75
2487	ASN330	OD1	-9.958	-3.151	-11.523
2488	ASN330	ND2	-9.893	-3.939	-13.632
2489	PRO331	N	-11.157	-0.201	-10.224
2490	PRO331	CA	-10.787	0.129	-8.843
2491	PRO331	C	-10.287	-1.061	-8.012
2492	PRO331	O	-9.994	-0.904	-6.822
2493	PRO331	CB	-12.044	0.673	-8.25
2494	PRO331	CG	-13.21	0.356	-9.172
2495	PRO331	CD	-12.608	-0.26	-10.416
2496	ASP332	N	-10.198	-2.236	-8.615
2497	ASP332	CA	-9.742	-3.417	-7.889
2498	ASP332	C	-8.267	-3.667	-8.179
2499	ASP332	O	-7.609	-4.447	-7.478
2500	ASP332	CB	-10.557	-4.617	-8.358
2501	ASP332	CG	-12.048	-4.356	-8.173
2502	ASP332	OD1	-12.43	-3.961	-7.08
2503	ASP332	OD2	-12.784	-4.566	-9.127
2504	THR333	N	-7.744	-2.97	-9.173
2505	THR333	CA	-6.339	-3.153	-9.535
2506	THR333	C	-5.433	-2.224	-8.735
2507	THR333	O	-5.283	-1.042	-9.06
2508	THR333	CB	-6.189	-2.877	-11.026
2509	THR333	OG1	-7.072	-3.748	-11.718
2510	THR333	CG2	-4.769	-3.147	-11.514
2511	PHE334	N	-4.84	-2.772	-7.688
2512	PHE334	CA	-3.868	-2.017	-6.89
2513	PHE334	C	-2.589	-1.762	-7.684
2514	PHE334	O	-1.817	-2.686	-7.979
2515	PHE334	CB	-3.543	-2.812	-5.63
2516	PHE334	CG	-2.485	-2.162	-4.744
2517	PHE334	CD1	-2.784	-1	-4.047
2518	PHE334	CD2	-1.221	-2.728	-4.638
2519	PHE334	CE1	-1.82	-0.404	-3.246
2520	PHE334	CE2	-0.256	-2.132	-3.837
2521	PHE334	CZ	-0.556	-0.969	-3.142
2522	ASP335	N	-2.407	-0.509	-8.064
2523	ASP335	CA	-1.206	-0.106	-8.794
2524	ASP335	C	-0.697	1.24	-8.283
2525	ASP335	O	-1.322	2.277	-8.525
2526	ASP335	CB	-1.55	-0.019	-10.277
2527	ASP335	CG	-0.276	0.2	-11.084
2528	ASP335	OD1	0.34	-0.792	-11.448
2529	ASP335	OD2	0.15	1.347	-11.159
2530	ILE336	N	0.532	1.249	-7.794
2531	ILE336	CA	1.118	2.426	-7.127
2532	ILE336	C	1.596	3.552	-8.058
2533	ILE336	O	2.207	4.512	-7.579
2534	ILE336	CB	2.303	1.948	-6.301
2535	ILE336	CG1	3.437	1.48	-7.203
2536	ILE336	CG2	1.873	0.817	-5.375

2537	ILE336	CD1	4.676	1.131	-6.396
2538	GLU337	N	1.41	3.407	-9.361
2539	GLU337	CA	1.712	4.496	-10.291
2540	GLU337	C	0.434	5.236	-10.681
2541	GLU337	O	0.487	6.246	-11.393
2542	GLU337	CB	2.393	3.936	-11.533
2543	GLU337	CG	3.788	3.412	-11.213
2544	GLU337	CD	4.442	2.871	-12.481
2545	GLU337	OE1	3.934	3.167	-13.552
2546	GLU337	OE2	5.372	2.089	-12.348
2547	ARG338	N	-0.697	4.719	-10.229
2548	ARG338	CA	-1.982	5.376	-10.464
2549	ARG338	C	-2.095	6.636	-9.615
2550	ARG338	O	-1.809	6.625	-8.412
2551	ARG338	CB	-3.085	4.393	-10.082
2552	ARG338	CG	-4.484	4.977	-10.234
2553	ARG338	CD	-5.532	3.961	-9.809
2554	ARG338	NE	-5.375	2.729	-10.591
2555	ARG338	CZ	-6.357	1.847	-10.77
2556	ARG338	NH1	-7.549	2.056	-10.207
2557	ARG338	NH2	-6.143	0.757	-11.509
2558	GLY339	N	-2.423	7.735	-10.271
2559	GLY339	CA	-2.685	8.98	-9.55
2560	GLY339	C	-4.038	8.895	-8.852
2561	GLY339	O	-5.086	9.045	-9.489
2562	ALA340	N	-3.994	8.767	-7.534
2563	ALA340	CA	-5.202	8.646	-6.691
2564	ALA340	C	-5.871	9.982	-6.335
2565	ALA340	O	-6.419	10.145	-5.237
2566	ALA340	CB	-4.817	7.907	-5.414
2567	ARG341	N	-5.844	10.917	-7.27
2568	ARG341	CA	-6.395	12.25	-7.043
2569	ARG341	C	-7.904	12.179	-6.87
2570	ARG341	O	-8.571	11.307	-7.436
2571	ARG341	CB	-6.045	13.131	-8.235
2572	ARG341	CG	-4.535	13.264	-8.387
2573	ARG341	CD	-4.175	14.135	-9.583
2574	ARG341	NE	-2.718	14.303	-9.691
2575	ARG341	CZ	-2.142	15.463	-10.016
2576	ARG341	NH1	-2.898	16.534	-10.271
2577	ARG341	NH2	-0.813	15.551	-10.092
2578	HIS342	N	-8.378	13.009	-5.954
2579	HIS342	CA	-9.801	13.12	-5.603
2580	HIS342	C	-10.342	11.888	-4.88
2581	HIS342	O	-11.547	11.621	-4.961
2582	HIS342	CB	-10.644	13.367	-6.855
2583	HIS342	CG	-10.32	14.641	-7.606
2584	HIS342	ND1	-10.757	15.877	-7.303
2585	HIS342	CD2	-9.536	14.758	-8.731
2586	HIS342	CE1	-10.259	16.758	-8.195
2587	HIS342	NE2	-9.504	16.064	-9.078
2588	HIS343	N	-9.49	11.15	-4.184
2589	HIS343	CA	-10.02	10.075	-3.346
2590	HIS343	C	-10.572	10.661	-2.053

2591	HIS343	O	-9.984	11.572	-1.455
2592	HIS343	CB	-8.988	8.965	-3.085
2593	HIS343	CG	-7.691	9.253	-2.333
2594	HIS343	ND1	-7.374	10.313	-1.562
2595	HIS343	CD2	-6.597	8.421	-2.319
2596	HIS343	CE1	-6.125	10.166	-1.079
2597	HIS343	NE2	-5.643	8.993	-1.549
2598	VAL344	N	-11.634	10.052	-1.563
2599	VAL344	CA	-12.278	10.521	-0.331
2600	VAL344	C	-11.732	9.82	0.915
2601	VAL344	O	-12.271	9.998	2.015
2602	VAL344	CB	-13.787	10.343	-0.45
2603	VAL344	CG1	-14.412	11.457	-1.282
2604	VAL344	CG2	-14.141	8.977	-1.019
2605	ALA345	N	-10.581	9.178	0.768
2606	ALA345	CA	-9.947	8.411	1.849
2607	ALA345	C	-9.419	9.24	3.02
2608	ALA345	O	-9.242	8.703	4.12
2609	ALA345	CB	-8.757	7.686	1.237
2610	PHE346	N	-9.169	10.518	2.787
2611	PHE346	CA	-8.763	11.424	3.867
2612	PHE346	C	-9.885	12.363	4.291
2613	PHE346	O	-9.652	13.29	5.083
2614	PHE346	CB	-7.571	12.253	3.409
2615	PHE346	CG	-6.223	11.583	3.635
2616	PHE346	CD1	-5.295	11.513	2.605
2617	PHE346	CD2	-5.921	11.048	4.881
2618	PHE346	CE1	-4.061	10.916	2.825
2619	PHE346	CE2	-4.687	10.451	5.101
2620	PHE346	CZ	-3.756	10.388	4.073
2621	GLY347	N	-11.068	12.169	3.731
2622	GLY347	CA	-12.177	13.091	3.979
2623	GLY347	C	-12.007	14.367	3.158
2624	GLY347	O	-10.882	14.764	2.825
2625	PHE348	N	-13.123	14.988	2.822
2626	PHE348	CA	-13.084	16.264	2.097
2627	PHE348	C	-13.98	17.307	2.752
2628	PHE348	O	-14.185	17.307	3.976
2629	PHE348	CB	-13.497	16.085	0.64
2630	PHE348	CG	-12.375	15.613	-0.285
2631	PHE348	CD1	-12.654	14.749	-1.333
2632	PHE348	CD2	-11.075	16.06	-0.081
2633	PHE348	CE1	-11.633	14.322	-2.172
2634	PHE348	CE2	-10.054	15.633	-0.918
2635	PHE348	CZ	-10.332	14.763	-1.963
2636	GLY349	N	-14.438	18.227	1.918
2637	GLY349	CA	-15.269	19.339	2.376
2638	GLY349	C	-14.484	20.194	3.353
2639	GLY349	O	-13.286	20.433	3.165
2640	VAL350	N	-15.121	20.525	4.458
2641	VAL350	CA	-14.426	21.29	5.493
2642	VAL350	C	-13.865	20.408	6.613
2643	VAL350	O	-12.964	20.854	7.327
2644	VAL350	CB	-15.384	22.334	6.062

2645	VAL350	CG1	-15.675	23.433	5.047
2646	VAL350	CG2	-16.682	21.709	6.561
2647	HIS351	N	-14.217	19.133	6.631
2648	HIS351	CA	-13.875	18.287	7.784
2649	HIS351	C	-12.75	17.284	7.532
2650	HIS351	O	-12.711	16.259	8.223
2651	HIS351	CB	-15.113	17.514	8.23
2652	HIS351	CG	-16.205	18.349	8.87
2653	HIS351	ND1	-16.137	18.987	10.054
2654	HIS351	CD2	-17.46	18.588	8.36
2655	HIS351	CE1	-17.304	19.619	10.29
2656	HIS351	NE2	-18.122	19.372	9.242
2657	GLN352	N	-11.876	17.53	6.568
2658	GLN352	CA	-10.852	16.518	6.26
2659	GLN352	C	-9.793	16.385	7.357
2660	GLN352	O	-9.716	17.193	8.291
2661	GLN352	CB	-10.178	16.785	4.923
2662	GLN352	CG	-9.244	17.98	4.902
2663	GLN352	CD	-8.308	17.803	3.712
2664	GLN352	OE1	-7.316	18.528	3.568
2665	GLN352	NE2	-8.572	16.766	2.934
2666	CYS353	N	-9.049	15.296	7.271
2667	CYS353	CA	-8.044	14.964	8.287
2668	CYS353	C	-6.883	15.962	8.319
2669	CYS353	O	-6.101	16.072	7.366
2670	CYS353	CB	-7.524	13.567	7.961
2671	CYS353	SG	-6.412	12.816	9.17
2672	LEU354	N	-6.724	16.61	9.464
2673	LEU354	CA	-5.607	17.549	9.666
2674	LEU354	C	-4.308	16.852	10.059
2675	LEU354	O	-3.224	17.358	9.747
2676	LEU354	CB	-5.967	18.561	10.748
2677	LEU354	CG	-6.805	19.7	10.188
2678	LEU354	CD1	-7.148	20.701	11.284
2679	LEU354	CD2	-6.054	20.396	9.057
2680	GLY355	N	-4.414	15.6	10.478
2681	GLY355	CA	-3.223	14.791	10.772
2682	GLY355	C	-2.835	13.936	9.566
2683	GLY355	O	-2.119	12.936	9.702
2684	GLN356	N	-3.078	14.499	8.393
2685	GLN356	CA	-2.896	13.81	7.119
2686	GLN356	C	-1.414	13.677	6.799
2687	GLN356	O	-0.939	12.562	6.544
2688	GLN356	CB	-3.598	14.696	6.094
2689	GLN356	CG	-3.657	14.117	4.691
2690	GLN356	CD	-4.524	15.024	3.818
2691	GLN356	OE1	-4.609	14.834	2.599
2692	GLN356	NE2	-5.231	15.939	4.463
2693	ASN357	N	-0.67	14.7	7.191
2694	ASN357	CA	0.781	14.7	7.005
2695	ASN357	C	1.476	13.761	7.989
2696	ASN357	O	2.328	12.977	7.554
2697	ASN357	CB	1.258	16.137	7.203
2698	ASN357	CG	2.78	16.244	7.261

2699	ASN357	OD1	3.324	16.808	8.217
2700	ASN357	ND2	3.444	15.745	6.233
2701	LEU358	N	0.896	13.592	9.166
2702	LEU358	CA	1.515	12.727	10.168
2703	LEU358	C	1.271	11.264	9.826
2704	LEU358	O	2.234	10.487	9.791
2705	LEU358	CB	0.908	13.034	11.53
2706	LEU358	CG	1.612	12.261	12.639
2707	LEU358	CD1	3.089	12.639	12.712
2708	LEU358	CD2	0.931	12.493	13.982
2709	ALA359	N	0.102	10.986	9.272
2710	ALA359	CA	-0.235	9.616	8.887
2711	ALA359	C	0.571	9.151	7.679
2712	ALA359	O	1.204	8.089	7.756
2713	ALA359	CB	-1.723	9.558	8.566
2714	ARG360	N	0.794	10.045	6.728
2715	ARG360	CA	1.585	9.681	5.546
2716	ARG360	C	3.078	9.603	5.853
2717	ARG360	O	3.747	8.677	5.374
2718	ARG360	CB	1.354	10.721	4.459
2719	ARG360	CG	-0.081	10.681	3.954
2720	ARG360	CD	-0.325	11.752	2.898
2721	ARG360	NE	-0.144	13.097	3.463
2722	ARG360	CZ	0.509	14.076	2.833
2723	ARG360	NH1	0.602	15.283	3.393
2724	ARG360	NH2	1.045	13.853	1.631
2725	LEU361	N	3.518	10.379	6.83
2726	LEU361	CA	4.921	10.356	7.239
2727	LEU361	C	5.238	9.078	8.005
2728	LEU361	O	6.174	8.36	7.628
2729	LEU361	CB	5.159	11.566	8.133
2730	LEU361	CG	6.612	11.69	8.572
2731	LEU361	CD1	7.537	11.811	7.365
2732	LEU361	CD2	6.778	12.888	9.498
2733	GLU362	N	4.306	8.658	8.846
2734	GLU362	CA	4.499	7.431	9.622
2735	GLU362	C	4.413	6.2	8.73
2736	GLU362	O	5.31	5.352	8.793
2737	GLU362	CB	3.418	7.347	10.694
2738	GLU362	CG	3.519	8.493	11.693
2739	GLU362	CD	2.341	8.447	12.662
2740	GLU362	OE1	1.268	8.901	12.284
2741	GLU362	OE2	2.517	7.891	13.736
2742	LEU363	N	3.541	6.253	7.736
2743	LEU363	CA	3.389	5.125	6.814
2744	LEU363	C	4.61	4.946	5.927
2745	LEU363	O	5.174	3.844	5.889
2746	LEU363	CB	2.184	5.364	5.914
2747	LEU363	CG	0.977	4.517	6.298
2748	LEU363	CD1	0.35	4.995	7.601
2749	LEU363	CD2	-0.056	4.54	5.179
2750	GLN364	N	5.151	6.047	5.432
2751	GLN364	CA	6.296	5.955	4.529
2752	GLN364	C	7.559	5.544	5.276

2753	GLN364	O	8.219	4.588	4.843
2754	GLN364	CB	6.505	7.308	3.86
2755	GLN364	CG	7.624	7.232	2.83
2756	GLN364	CD	7.846	8.592	2.181
2757	GLN364	OE1	7.741	9.637	2.835
2758	GLN364	NE2	8.108	8.565	0.886
2759	ILE365	N	7.707	6.019	6.503
2760	ILE365	CA	8.879	5.644	7.298
2761	ILE365	C	8.835	4.171	7.691
2762	ILE365	O	9.772	3.438	7.339
2763	ILE365	CB	8.94	6.511	8.554
2764	ILE365	CG1	9.202	7.973	8.208
2765	ILE365	CG2	10.012	5.996	9.506
2766	ILE365	CD1	10.539	8.151	7.497
2767	VAL366	N	7.667	3.695	8.099
2768	VAL366	CA	7.555	2.301	8.53
2769	VAL366	C	7.703	1.335	7.361
2770	VAL366	O	8.611	0.497	7.417
2771	VAL366	CB	6.21	2.076	9.217
2772	VAL366	CG1	6.011	0.606	9.565
2773	VAL366	CG2	6.085	2.923	10.477
2774	PHE367	N	7.094	1.641	6.225
2775	PHE367	CA	7.145	0.701	5.097
2776	PHE367	C	8.524	0.663	4.453
2777	PHE367	O	9.066	-0.434	4.254
2778	PHE367	CB	6.125	1.099	4.034
2779	PHE367	CG	4.662	1.012	4.458
2780	PHE367	CD1	3.726	1.83	3.841
2781	PHE367	CD2	4.258	0.112	5.435
2782	PHE367	CE1	2.391	1.767	4.216
2783	PHE367	CE2	2.924	0.052	5.813
2784	PHE367	CZ	1.99	0.88	5.206
2785	ASP368	N	9.187	1.808	4.423
2786	ASP368	CA	10.522	1.869	3.83
2787	ASP368	C	11.52	1.102	4.686
2788	ASP368	O	12.115	0.138	4.185
2789	ASP368	CB	10.964	3.326	3.707
2790	ASP368	CG	10.101	4.09	2.701
2791	ASP368	OD1	10.208	5.31	2.678
2792	ASP368	OD2	9.508	3.443	1.847
2793	THR369	N	11.438	1.285	5.995
2794	THR369	CA	12.381	0.606	6.892
2795	THR369	C	12.07	-0.88	7.076
2796	THR369	O	13.004	-1.658	7.287
2797	THR369	CB	12.376	1.294	8.252
2798	THR369	OG1	11.058	1.242	8.778
2799	THR369	CG2	12.797	2.756	8.149
2800	LEU370	N	10.848	-1.302	6.793
2801	LEU370	CA	10.523	-2.729	6.862
2802	LEU370	C	11.145	-3.486	5.703
2803	LEU370	O	12.038	-4.319	5.916
2804	LEU370	CB	9.012	-2.919	6.78
2805	LEU370	CG	8.302	-2.463	8.044
2806	LEU370	CD1	6.792	-2.589	7.882

2807	LEU370	CD2	8.79	-3.256	9.248
2808	PHE371	N	10.872	-3.006	4.502
2809	PHE371	CA	11.266	-3.75	3.303
2810	PHE371	C	12.728	-3.529	2.918
2811	PHE371	O	13.332	-4.398	2.278
2812	PHE371	CB	10.333	-3.34	2.169
2813	PHE371	CG	8.861	-3.634	2.463
2814	PHE371	CD1	7.935	-2.599	2.503
2815	PHE371	CD2	8.447	-4.94	2.692
2816	PHE371	CE1	6.601	-2.867	2.784
2817	PHE371	CE2	7.112	-5.209	2.971
2818	PHE371	CZ	6.19	-4.172	3.019
2819	ARG372	N	13.335	-2.472	3.436
2820	ARG372	CA	14.773	-2.281	3.231
2821	ARG372	C	15.606	-2.901	4.353
2822	ARG372	O	16.834	-2.982	4.229
2823	ARG372	CB	15.084	-0.795	3.116
2824	ARG372	CG	14.397	-0.176	1.904
2825	ARG372	CD	14.777	1.291	1.76
2826	ARG372	NE	14.497	2.015	3.008
2827	ARG372	CZ	14.919	3.257	3.251
2828	ARG372	NH1	14.646	3.835	4.423
2829	ARG372	NH2	15.631	3.911	2.331
2830	ARG373	N	14.958	-3.347	5.418
2831	ARG373	CA	15.671	-4.087	6.457
2832	ARG373	C	15.659	-5.559	6.09
2833	ARG373	O	16.694	-6.238	6.097
2834	ARG373	CB	14.937	-3.926	7.783
2835	ARG373	CG	15.657	-4.637	8.922
2836	ARG373	CD	16.912	-3.879	9.335
2837	ARG373	NE	16.548	-2.554	9.862
2838	ARG373	CZ	16.405	-2.304	11.165
2839	ARG373	NH1	16.663	-3.261	12.059
2840	ARG373	NH2	16.046	-1.087	11.576
2841	VAL374	N	14.474	-6.032	5.749
2842	VAL374	CA	14.314	-7.425	5.338
2843	VAL374	C	13.644	-7.499	3.971
2844	VAL374	O	12.43	-7.307	3.841
2845	VAL374	CB	13.473	-8.164	6.376
2846	VAL374	CG1	13.297	-9.625	5.984
2847	VAL374	CG2	14.086	-8.075	7.77
2848	PRO375	N	14.432	-7.873	2.976
2849	PRO375	CA	13.929	-8.036	1.606
2850	PRO375	C	13.088	-9.304	1.369
2851	PRO375	O	12.539	-9.472	0.275
2852	PRO375	CB	15.165	-8.072	0.76
2853	PRO375	CG	16.384	-8.221	1.658
2854	PRO375	CD	15.865	-8.159	3.084
2855	GLY376	N	12.945	-10.158	2.371
2856	GLY376	CA	12.162	-11.386	2.21
2857	GLY376	C	11.071	-11.52	3.271
2858	GLY376	O	11.012	-12.523	3.992
2859	ILE377	N	10.225	-10.508	3.367
2860	ILE377	CA	9.092	-10.568	4.299

2861	ILE377	C	7.921	-11.295	3.645
2862	ILE377	O	7.217	-10.731	2.801
2863	ILE377	CB	8.663	-9.148	4.656
2864	ILE377	CG1	9.836	-8.352	5.203
2865	ILE377	CG2	7.529	-9.169	5.674
2866	ILE377	CD1	9.433	-6.919	5.526
2867	ARG378	N	7.743	-12.55	4.009
2868	ARG378	CA	6.648	-13.342	3.451
2869	ARG378	C	5.468	-13.417	4.409
2870	ARG378	O	5.629	-13.304	5.627
2871	ARG378	CB	7.186	-14.734	3.163
2872	ARG378	CG	8.265	-14.671	2.089
2873	ARG378	CD	8.975	-16.01	1.929
2874	ARG378	NE	9.756	-16.33	3.134
2875	ARG378	CZ	9.57	-17.431	3.864
2876	ARG378	NH1	8.587	-18.28	3.556
2877	ARG378	NH2	10.338	-17.659	4.931
2878	ILE379	N	4.277	-13.531	3.854
2879	ILE379	CA	3.096	-13.713	4.703
2880	ILE379	C	3.14	-15.13	5.272
2881	ILE379	O	3.519	-16.07	4.563
2882	ILE379	CB	1.841	-13.536	3.855
2883	ILE379	CG1	2.108	-12.589	2.692
2884	ILE379	CG2	0.702	-12.984	4.709
2885	ILE379	CD1	0.882	-12.447	1.798
2886	ALA380	N	2.872	-15.267	6.56
2887	ALA380	CA	2.895	-16.598	7.174
2888	ALA380	C	1.533	-17.277	7.07
2889	ALA380	O	1.435	-18.51	7.097
2890	ALA380	CB	3.306	-16.471	8.635
2891	VAL381	N	0.498	-16.47	6.917
2892	VAL381	CA	-0.839	-17.005	6.651
2893	VAL381	C	-1.231	-16.745	5.2
2894	VAL381	O	-0.782	-15.768	4.59
2895	VAL381	CB	-1.847	-16.359	7.599
2896	VAL381	CG1	-1.705	-16.897	9.018
2897	VAL381	CG2	-1.747	-14.839	7.57
2898	PRO382	N	-1.999	-17.662	4.635
2899	PRO382	CA	-2.615	-17.424	3.329
2900	PRO382	C	-3.477	-16.166	3.352
2901	PRO382	O	-4.045	-15.802	4.391
2902	PRO382	CB	-3.422	-18.651	3.039
2903	PRO382	CG	-3.29	-19.627	4.198
2904	PRO382	CD	-2.414	-18.938	5.231
2905	VAL383	N	-3.721	-15.621	2.172
2906	VAL383	CA	-4.415	-14.327	2.051
2907	VAL383	C	-5.892	-14.388	2.452
2908	VAL383	O	-6.376	-13.473	3.126
2909	VAL383	CB	-4.302	-13.886	0.593
2910	VAL383	CG1	-5.05	-12.578	0.343
2911	VAL383	CG2	-2.838	-13.751	0.177
2912	ASP384	N	-6.478	-15.572	2.355
2913	ASP384	CA	-7.876	-15.767	2.759
2914	ASP384	C	-8.031	-15.962	4.271

2915	ASP384	O	-9.156	-16.094	4.761
2916	ASP384	CB	-8.42	-17.003	2.048
2917	ASP384	CG	-8.293	-16.849	0.534
2918	ASP384	OD1	-9.1	-16.128	-0.032
2919	ASP384	OD2	-7.312	-17.346	-0.002
2920	GLU385	N	-6.926	-15.995	5
2921	GLU385	CA	-6.994	-16.177	6.448
2922	GLU385	C	-6.674	-14.884	7.194
2923	GLU385	O	-6.638	-14.896	8.429
2924	GLU385	CB	-6.01	-17.259	6.874
2925	GLU385	CG	-6.219	-18.561	6.111
2926	GLU385	CD	-7.651	-19.079	6.248
2927	GLU385	OE1	-8.017	-19.462	7.349
2928	GLU385	OE2	-8.266	-19.256	5.205
2929	LEU386	N	-6.406	-13.81	6.463
2930	LEU386	CA	-6.082	-12.519	7.093
2931	LEU386	C	-7.266	-11.953	7.874
2932	LEU386	O	-8.342	-11.71	7.315
2933	LEU386	CB	-5.676	-11.542	5.996
2934	LEU386	CG	-4.348	-11.943	5.365
2935	LEU386	CD1	-4.081	-11.153	4.091
2936	LEU386	CD2	-3.204	-11.773	6.357
2937	PRO387	N	-7.063	-11.798	9.173
2938	PRO387	CA	-8.132	-11.39	10.091
2939	PRO387	C	-8.419	-9.89	10.047
2940	PRO387	O	-7.84	-9.095	10.805
2941	PRO387	CB	-7.647	-11.801	11.445
2942	PRO387	CG	-6.191	-12.224	11.339
2943	PRO387	CD	-5.817	-12.105	9.873
2944	PHE388	N	-9.314	-9.528	9.143
2945	PHE388	CA	-9.775	-8.145	9.012
2946	PHE388	C	-10.688	-7.79	10.176
2947	PHE388	O	-11.522	-8.597	10.603
2948	PHE388	CB	-10.558	-7.999	7.709
2949	PHE388	CG	-9.785	-8.343	6.437
2950	PHE388	CD1	-8.78	-7.498	5.987
2951	PHE388	CD2	-10.097	-9.492	5.721
2952	PHE388	CE1	-8.076	-7.809	4.831
2953	PHE388	CE2	-9.393	-9.804	4.565
2954	PHE388	CZ	-8.381	-8.963	4.121
2955	LYS389	N	-10.5	-6.599	10.707
2956	LYS389	CA	-11.364	-6.141	11.792
2957	LYS389	C	-12.626	-5.52	11.203
2958	LYS389	O	-12.542	-4.581	10.4
2959	LYS389	CB	-10.611	-5.115	12.633
2960	LYS389	CG	-11.439	-4.708	13.847
2961	LYS389	CD	-10.677	-3.763	14.767
2962	LYS389	CE	-11.487	-3.466	16.023
2963	LYS389	NZ	-10.719	-2.637	16.96
2964	HIS390	N	-13.775	-6.068	11.571
2965	HIS390	CA	-15.055	-5.523	11.102
2966	HIS390	C	-15.385	-4.226	11.836
2967	HIS390	O	-15.845	-4.213	12.983
2968	HIS390	CB	-16.162	-6.548	11.316

2969	HIS390	CG	-17.525	-6.094	10.826
2970	HIS390	ND1	-17.895	-5.893	9.545
2971	HIS390	CD2	-18.62	-5.81	11.607
2972	HIS390	CE1	-19.181	-5.487	9.511
2973	HIS390	NE2	-19.629	-5.437	10.786
2974	ASP391	N	-15.053	-3.138	11.167
2975	ASP391	CA	-15.269	-1.789	11.683
2976	ASP391	C	-15.392	-0.871	10.48
2977	ASP391	O	-14.395	-0.539	9.835
2978	ASP391	CB	-14.068	-1.414	12.553
2979	ASP391	CG	-14.172	-0.02	13.18
2980	ASP391	OD1	-14.984	0.771	12.707
2981	ASP391	OD2	-13.241	0.324	13.884
2982	SER392	N	-16.582	-0.335	10.283
2983	SER392	CA	-16.835	0.448	9.075
2984	SER392	C	-16.261	1.863	9.129
2985	SER392	O	-15.99	2.431	8.07
2986	SER392	CB	-18.342	0.537	8.868
2987	SER392	OG	-18.876	1.383	9.878
2988	THR393	N	-15.944	2.392	10.297
2989	THR393	CA	-15.451	3.768	10.313
2990	THR393	C	-13.931	3.822	10.468
2991	THR393	O	-13.294	4.722	9.909
2992	THR393	CB	-16.183	4.53	11.411
2993	THR393	OG1	-17.557	4.561	11.04
2994	THR393	CG2	-15.703	5.972	11.528
2995	ILE394	N	-13.365	2.816	11.118
2996	ILE394	CA	-11.899	2.665	11.203
2997	ILE394	C	-11.525	1.204	10.92
2998	ILE394	O	-11.205	0.419	11.824
2999	ILE394	CB	-11.37	3.095	12.577
3000	ILE394	CG1	-11.744	4.533	12.921
3001	ILE394	CG2	-9.847	2.978	12.624
3002	ILE394	CD1	-10.977	5.529	12.055
3003	TYR395	N	-11.59	0.854	9.649
3004	TYR395	CA	-11.29	-0.503	9.179
3005	TYR395	C	-9.792	-0.786	9.302
3006	TYR395	O	-8.997	0.149	9.447
3007	TYR395	CB	-11.747	-0.572	7.721
3008	TYR395	CG	-11.784	-1.967	7.101
3009	TYR395	CD1	-10.958	-2.272	6.026
3010	TYR395	CD2	-12.648	-2.927	7.612
3011	TYR395	CE1	-10.991	-3.543	5.465
3012	TYR395	CE2	-12.682	-4.199	7.052
3013	TYR395	CZ	-11.852	-4.502	5.982
3014	TYR395	OH	-11.882	-5.763	5.427
3015	GLY396	N	-9.433	-2.053	9.421
3016	GLY396	CA	-8.007	-2.401	9.468
3017	GLY396	C	-7.732	-3.871	9.759
3018	GLY396	O	-8.601	-4.74	9.609
3019	LEU397	N	-6.493	-4.132	10.134
3020	LEU397	CA	-6.031	-5.497	10.406
3021	LEU397	C	-5.334	-5.577	11.751
3022	LEU397	O	-4.297	-4.938	11.961

3023	LEU397	CB	-5.051	-5.894	9.311
3024	LEU397	CG	-5.773	-6.502	8.12
3025	LEU397	CD1	-5.037	-6.225	6.822
3026	LEU397	CD2	-5.979	-7.996	8.325
3027	HIS398	N	-5.87	-6.402	12.634
3028	HIS398	CA	-5.274	-6.514	13.967
3029	HIS398	C	-4.348	-7.718	14.107
3030	HIS398	O	-3.651	-7.848	15.12
3031	HIS398	CB	-6.363	-6.528	15.033
3032	HIS398	CG	-6.737	-5.14	15.525
3033	HIS398	ND1	-7.052	-4.804	16.79
3034	HIS398	CD2	-6.795	-3.984	14.781
3035	HIS398	CE1	-7.311	-3.482	16.851
3036	HIS398	NE2	-7.152	-2.975	15.607
3037	ALA399	N	-4.306	-8.567	13.094
3038	ALA399	CA	-3.343	-9.671	13.12
3039	ALA399	C	-2.7	-9.903	11.756
3040	ALA399	O	-3.373	-10.014	10.724
3041	ALA399	CB	-4.014	-10.936	13.633
3042	LEU400	N	-1.383	-10.004	11.794
3043	LEU400	CA	-0.567	-10.204	10.589
3044	LEU400	C	0.772	-10.856	10.935
3045	LEU400	O	1.712	-10.165	11.35
3046	LEU400	CB	-0.307	-8.845	9.946
3047	LEU400	CG	0.615	-8.952	8.736
3048	LEU400	CD1	0.005	-9.826	7.644
3049	LEU400	CD2	0.973	-7.572	8.197
3050	PRO401	N	0.815	-12.178	10.881
3051	PRO401	CA	2.084	-12.9	10.974
3052	PRO401	C	2.88	-12.822	9.671
3053	PRO401	O	2.413	-13.242	8.602
3054	PRO401	CB	1.686	-14.312	11.269
3055	PRO401	CG	0.197	-14.466	10.993
3056	PRO401	CD	-0.308	-13.08	10.625
3057	VAL402	N	4.074	-12.267	9.78
3058	VAL402	CA	5.008	-12.183	8.653
3059	VAL402	C	6.358	-12.814	8.998
3060	VAL402	O	7.008	-12.485	9.998
3061	VAL402	CB	5.194	-10.723	8.25
3062	VAL402	CG1	3.968	-10.185	7.523
3063	VAL402	CG2	5.553	-9.84	9.44
3064	THR403	N	6.772	-13.729	8.146
3065	THR403	CA	8.039	-14.428	8.342
3066	THR403	C	9.135	-13.709	7.571
3067	THR403	O	9.102	-13.66	6.335
3068	THR403	CB	7.888	-15.853	7.827
3069	THR403	OG1	6.715	-16.403	8.406
3070	THR403	CG2	9.077	-16.723	8.22
3071	TRP404	N	10.089	-13.156	8.298
3072	TRP404	CA	11.177	-12.406	7.66
3073	TRP404	C	12.136	-13.344	6.931
3074	TRP404	O	12.984	-12.835	6.21
3075	TRP404	CB	11.969	-11.654	8.719
3076	TRP404	CG	11.163	-10.949	9.79

3077	TRP404	CD1	10.886	-11.444	11.043
3078	TRP404	CD2	10.559	-9.637	9.729
3079	TRP404	NE1	10.155	-10.524	11.721
3080	TRP404	CE2	9.943	-9.428	10.972
3081	TRP404	CE3	10.506	-8.656	8.749
3082	TRP404	CZ2	9.278	-8.237	11.225
3083	TRP404	CZ3	9.838	-7.468	9.009
3084	TRP404	CH2	9.226	-7.257	10.239
3085	TRP404	OXT	12.117	-14.53	7.239
3086	HEM1	FE	-8.08	12.05	10.226
3087	HEM1	NA	-9.653	12.085	9.078
3088	HEM1	C1A	-10.7	13.004	9.077
3089	HEM1	C2A	-11.687	12.681	8.118
3090	HEM1	C3A	-11.292	11.525	7.568
3091	HEM1	[illegible]A	-10.019	11.174	8.129
3092	HEM1	CHB	-9.224	10.115	7.699
3093	HEM1	C1B	-7.931	9.83	8.181
3094	HEM1	NB	-7.308	10.582	9.182
3095	HEM1	C4B	-6.086	9.964	9.364
3096	HEM1	C3B	-5.946	8.85	8.506
3097	HEM1	C2B	-7.068	8.771	7.746
3098	HEM1	CMB	-7.416	7.755	6.682
3099	HEM1	CAB	-4.833	8.031	8.591
3100	HEM1	CBB	-4.44	7.051	7.74
3101	HEM1	CHC	-5.212	10.298	10.374
3102	HEM1	C1C	-5.439	11.223	11.336
3103	HEM1	NC	-6.519	12.039	11.384
3104	HEM1	C4C	-6.227	12.887	12.426
3105	HEM1	C3C	-4.926	12.636	13.002
3106	HEM1	C2C	-4.491	11.556	12.313
3107	HEM1	CMC	-3.265	10.712	12.532
3108	HEM1	CAC	-4.462	13.435	14.055
3109	HEM1	CBC	-3.452	13.231	14.936
3110	HEM1	CHD	-7.061	13.855	12.91
3111	HEM1	C1D	-8.237	14.203	12.292
3112	HEM1	ND	-8.777	13.572	11.18
3113	HEM1	C4D	-9.915	14.313	10.916
3114	HEM1	C3D	-10.045	15.413	11.808
3115	HEM1	C2D	-9.006	15.334	12.673
3116	HEM1	CMD	-8.71	16.241	13.844
3117	HEM1	CAD	-11.178	16.421	11.802
3118	HEM1	CBD	-10.91	17.624	10.918
3119	HEM1	CGD	-12.079	18.574	10.862
3120	HEM1	O1D	-13.198	18.167	11.204
3121	HEM1	O2D	-11.889	19.736	10.477
3122	HEM1	CHA	-10.849	14.026	9.961
3123	HEM1	CMA	-12.005	10.703	6.498
3124	HEM1	CAA	-12.907	13.51	7.748
3125	HEM1	CBA	-14.087	13.112	8.645
3126	HEM1	CGA	-15.442	13.596	8.14
3127	HEM1	O1A	-15.522	14.131	7.009
3128	HEM1	O2A	-16.439	13.4	8.866

What is Claimed is:

1. An isolated nucleic acid sequence encoding epothilone B hydroxylase or a mutant or variant thereof.

2. The isolated nucleic acid sequence of claim 1 comprising SEQ ID NO: 1, 30, 32, 34, 36, 37, 38, 39, 40, 41, 42, 60, 62, 64, 66, 68, 72 or 74.

3. The isolated nucleic acid sequence of claim 1 comprising SEQ ID NO:1.

4. The isolated nucleic acid sequence of claim 1 encoding a mutant with at least one amino acid substitution in an active site of the epothilone B hydroxylase enzyme.

5. The isolated nucleic acid sequence of claim 1 encoding a mutant with at least one amino acid substitution at amino acid GLU31, ARG67, ARG88, ILE92, ALA93, VAL106, ILE130, ALA140, MET176, PHE190, GLU 231, SER294, PHE237, or ILE365 of SEQ ID NO:2.

6. The isolated nucleic acid sequence of claim 1 encoding a mutant with at least one amino acid substitution at amino acid LEU39, GLN43, ALA45, MET57, LEU58, HIS62, PHE63, SER64, SER65, ASP66, ARG67, GLN68, SER69, LEU74, MET75, VAL76, ALA77, ARG78, GLN79, ILE80, ASP84, LYS85, PRO86, PHE87, ARG88, PRO89, SER90, LEU91, ILE92, ALA93, MET94, ASP95, HIS99, ARG103, PHE110, ILE155, PHE169, GLN170, CYS172, SER173, SER174, ARG175, MET176, LEU177, SER178, ARG179, ARG186, PHE190, LEU193, VAL233, GLY234, LEU235, ALA236, PHE237, LEU238, LEU239, LEU240, ILE241, ALA242, GLY243, HIS244, GLU245, THR246, THR247, ALA248, ASN249, MET250, LEU283, THR287, ILE288, ALA289, GLU290, THR291, ALA292, THR293, SER294, ARG295, PHE296, ALA297, THR298, GLU312, GLY313, VAL314, VAL315, GLY316, VAL344, ALA345, PHE346, GLY347, PHE348, VAL350, HIS351, GLN352, CYS353, LEU354, GLY355, GLN356, LEU358,

ALA359, GLU362, LYS389, ASP391, SER392, THR393, ILE394, or TYR395 of SEQ ID NO:2.

7. The isolated nucleic acid sequence of claim 1 encoding a variant comprising SEQ ID NO:43, 44, 45, 46, 47, 48 or 49.

8. A polypeptide encoded by the isolated nucleic acid sequence of claim 1.

9. An isolated nucleic acid molecule that is capable of hybridizing to a nucleic acid sequence of claim 2, or to the complementary sequence of said nucleic acid sequence, under hybridization conditions of 3X SSC at 65°C for 16 hours, said isolated nucleic acid molecule being capable of remaining hybridized to said nucleic acid sequence, or to the complementary sequence of said nucleic acid sequence, under wash conditions of 0.5X SSC, 55°C for 30 minutes.

10. An isolated polypeptide comprising SEQ ID NO:2.

11. An isolated mutant polypeptide of epothilone B hydroxylase of SEQ ID NO:2 comprising an amino acid sequence with at least one amino acid substitution in an active site of epothilone B hydroxylase enzyme of SEQ ID NO:2.

12. An isolated mutant polypeptide of epothilone B hydroxylase of SEQ ID NO:2 comprising an amino acid sequence with at least one amino acid substitution at amino acid GLU31, ARG67, ARG88, ILE92, ALA93, VAL106, ILE130, ALA140, MET176, PHE190, GLU 231, SER294, PHE237, or ILE365 of SEQ ID NO:2.

13. An isolated mutant polypeptide of epothilone B hydroxylase of SEQ ID NO:2 comprising an amino acid sequence with at least one amino acid substitution at amino acid LEU39, GLN43, ALA45, MET57, LEU58, HIS62, PHE63, SER64, SER65, ASP66, ARG67, GLN68, SER69, LEU74, MET75, VAL76, ALA77, ARG78, GLN79, ILE80, ASP84, LYS85, PRO86, PHE87, ARG88, PRO89, SER90, LEU91, ILE92, ALA93, MET94, ASP95, HIS99, ARG103, PHE110, ILE155,

PHE169, GLN170, CYS172, SER173, SER174, ARG175, MET176, LEU177, SER178, ARG179, ARG186, PHE190, LEU193, VAL233, GLY234, LEU235, ALA236, PHE237, LEU238, LEU239, LEU240, ILE241, ALA242, GLY243, HIS244, GLU245, THR246, THR247, ALA248, ASN249, MET250, LEU283, THR287, ILE288, ALA289, GLU290, THR291, ALA292, THR293, SER294, ARG295, PHE296, ALA297, THR298, GLU312, GLY313, VAL314, VAL315, GLY316, VAL344, ALA345, PHE346, GLY347, PHE348, VAL350, HIS351, GLN352, CYS353, LEU354, GLY355, GLN356, LEU358, ALA359, GLU362, LYS389, ASP391, SER392, THR393, ILE394, or TYR395 of SEQ ID NO:2.

14. An isolated mutant polypeptide of epothilone B hydroxylase comprising SEQ ID NO: 31, 33, 35, 61, 63, 65, 67, 69, 71, 73 or 75.

15. An isolated variant polypeptide of epothilone B hydroxylase comprising SEQ ID NO: 43, 44, 45, 46, 47, 48 or 49.

16. An isolated nucleic acid sequence encoding a ferredoxin.

17. The isolated nucleic acid sequence of claim 16 comprising SEQ ID NO:3.

18. A polypeptide encoded by the isolated nucleic acid sequence of claim 16.

19. An isolated nucleic acid molecule that is capable of hybridizing to the nucleic acid sequence set forth in SEQ ID NO:3, or to the complementary sequence of the nucleic acid sequence set forth in SEQ ID NO:3, under hybridization conditions of 3X SSC at 65°C for 16 hours, said isolated nucleic acid molecule being capable of remaining hybridized to the nucleic acid sequence set forth in SEQ ID NO:3, or to the complementary sequence of the nucleic acid sequence set forth in SEQ ID NO:3, under wash conditions of 0.5X SSC, 55°C for 30 minutes.

20. A vector comprising the isolated nucleic acid sequence of claim 1.

21. The vector of claim 20 further comprising an isolated nucleic acid sequence encoding a ferredoxin.

22. A host cell comprising the vector of claim 20.

23. A host cell comprising the vector of claim 21.

24. A method for producing recombinant microorganisms which hydroxylate epothilones having a terminal alkyl group to produce epothilones having a terminal hydroxyalkyl group, said method comprising transfecting a microorganism with the vector of claim 20 or 21.

25. A recombinantly produced microorganism that hydroxylates epothilones having a terminal alkyl group to produce epothilones having a terminal hydroxyalkyl group.

26. The recombinantly produced microorganism of claim 25 wherein said microorganism expresses a nucleic acid sequence of SEQ ID NO: 1, [illegible], 32, 34, 36, 37, 38, 39, 40, 41, 42, 60, 62, 64, 66, 68, 72 or 74.

27. A method for the preparation of at least one epothilone of the following formula I

$$HO\text{-}CH_2\text{-}(A_1)_n\text{-}(Q)_m\text{-}(A_2)_o\text{-}E \qquad (I)$$

where

A_1 and A_2 are independently selected from the group of optionally substituted C_1-C_3 alkyl and alkenyl;

Q is an optionally substituted ring system containing one to three rings and at least one carbon to carbon double bond in at least one ring;

n, m, and o are integers selected from the group consisting of zero and 1, where at least one of m or n or o is 1; and

E is an epothilone core;

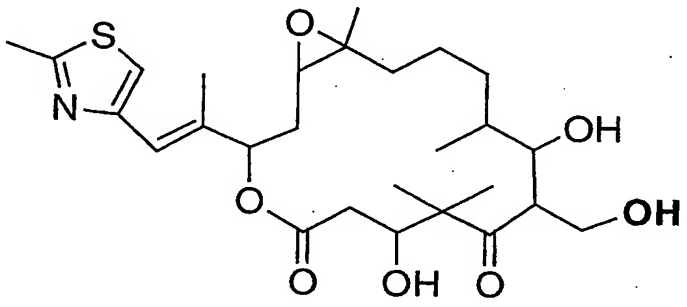
comprising the steps of contacting at least one epothilone of the following formula II

$$CH_3\text{-}(A_1)_n\text{-}(Q)_m\text{-}(A_2)_o\text{-}E \qquad (II)$$

where A_1, Q, A_2, E, n, m, and o are defined as above;

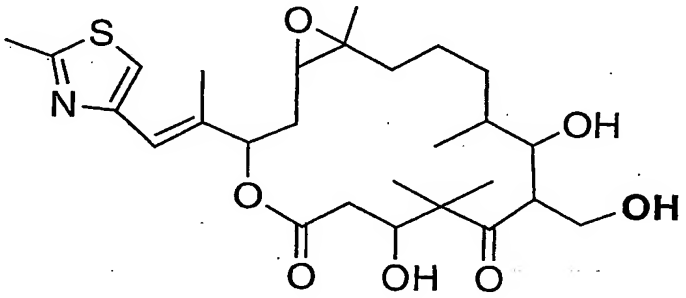
with a recombinantly produced microorganism, or an enzyme derived therefrom, which is capable of selectively catalyzing the hydroxylation of Formula II, and effecting said hydroxylation.

28. A method for the preparation of an epothilone analog of Formula A



said method comprising biotransforming epothilone B to the epothilone analog of Formula A by incubation with a mutant epothilone B hydroxylase enzyme comprising SEQ ID NO:31.

29. A compound of Formula A



or a pharmaceutically acceptable salt thereof.

30. A homology model of epothilone B hydroxylase having a root mean square deviation of conserved residue backbone atoms of less than about 4.0 Å when superimposed on a corresponding backbone atoms described by structure coordinates listed in Appendix 1.

31. A method for producing a mutant with altered biological properties, function, yield of a desired product, rate of reaction, substrate specificity, or activity as compared to epothilone B hydroxylase, said method comprising the steps of: identifying an amino acid of SEQ ID NO:2 to mutate; and mutating the identified amino acid to create a mutant protein.

32. The method of claim 31 wherein a homology model of epothilone B hydroxylase having a root mean square deviation of conserved residue backbone atoms of less than about 4.0 Å when superimposed on a corresponding backbone atoms described by structure coordinates listed in Appendix 1 is used to identify an amino acid of SEQ ID NO: 2 to mutate.

33. The method of claim 31 wherein the identified amino acid is LEU39, GLN43, ALA45, MET57, LEU58, HIS62, PHE63, SER64, SER65, ASP66, ARG67, GLN68, SER69, LEU74, MET75, VAL76, ALA77, ARG78, GLN79, ILE80, ASP84, LYS85, PRO86, PHE87, ARG88, PRO89, SER90, LEU91, ILE92, ALA93, MET94, ASP95, HIS99, ARG103, PHE110, ILE155, PHE169, GLN170, CYS172, SER173, SER174, ARG175, MET176, LEU177, SER178, ARG179, ARG186, PHE190, LEU193, VAL233, GLY234, LEU235, ALA236, PHE237, LEU238, LEU239, LEU240, ILE241, ALA242, GLY243, HIS244, GLU245, THR246, THR247, ALA248, ASN249, MET250, LEU283, THR287, ILE288, ALA289, GLU290, THR291, ALA292, THR293, SER294, ARG295, PHE296, ALA297, THR298, GLU312, GLY313, VAL314, VAL315, GLY316, VAL344, ALA345, PHE346, GLY347, PHE348, VAL350, HIS351, GLN352, CYS353, LEU354, GLY355, GLN356, LEU358, ALA359, GLU362, LYS389, ASP391, SER392, THR393, ILE394, or TYR395 of SEQ ID NO:2.

34. The method of claim 31 wherein the identified amino acid is GLU31, ARG67, ARG88, ILE92, ALA93, VAL106, ILE130, ALA140, MET176, PHE190, GLU 231, SER294, PHE237, or ILE365 of SEQ ID NO:2.

35. The method of claim 31 wherein the mutant protein improves yield of a desired product as compared to the yield of a desired product obtained using epothilone B hydroxylase.

36. The method of claim 35 wherein the desired product is epothilone F.

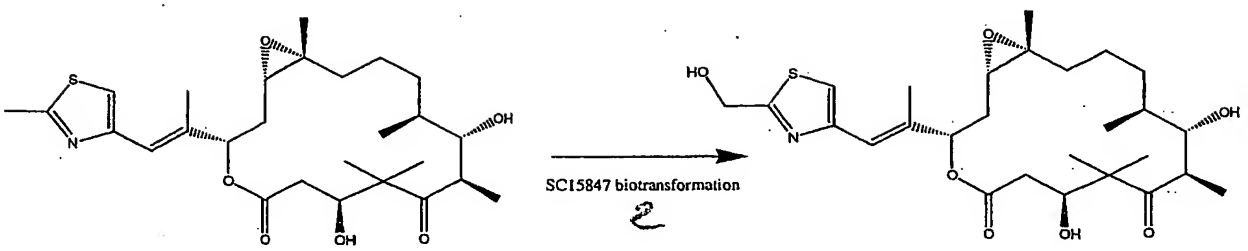
37. The method of claim 31 wherein the mutant improves the rate of reaction as compared to the rate of reaction using epothilone B hydroxylase.

38. The method of claim 31 wherein the mutant exhibits altered substrate specificity as compared to substrate specificity of epothilone B hydroxylase.

39. The method of claim 38 wherein amino acid SER294 is mutated.

40. The method of claim 31 wherein the mutant exhibits essentially similar biological activity or function to epothilone B hydroxylase.

41. A machine-readable data storage medium comprising a data storage material encoded with structure coordinates set forth in Appendix 1.



epothilone B

epothilone F

FIG. 1

Alignment used to design primers P450-1^{+} and P450-1a^{+}

STMSUACB	tcctcatcgccggccacgagac	(SEQ ID NO:5)
STMSUBCB	tgctggtcgccggccacgagac	(SEQ ID NO:6)
3702259	tgctcatcaccggccaggacac	(SEQ ID NO:7)
SSU65940	--ctgttcgccgggcacgactc	(SEQ ID NO:8)
STMOLEP	tgctcatcgcgggccacgagac	(SEQ ID NO:9)
SERCP450A	tgctggtcgccgggcacgagac	(SEQ ID NO:10)

Alignment used to design primers P450-2^{+} and P450-2^{-}

STMSUACB	cggcgcggtggaggaactgct	(SEQ ID NO:11)
STMSUBCB	gggcgccgtcgaggagctgct	(SEQ ID NO:12)
3702259	ccgcaccctggaggagctgct	(SEQ ID NO:13)
SSU65940	cggcgcggtcgaggagatgct	(SEQ ID NO:14)
STMOLEP	cgcggcggtggaggagatgct	(SEQ ID NO:15)
SERCP450A	cggcgcgatcgaggagaccct	(SEQ ID NO:16)

Alignment used to design primer P450-3^{-}

STMSUACB	ttcggcttcggcgtgcaccagtgcctgggc	(SEQ ID NO:17)
STMSUBCB	ttcggcttcggcgtccaccagtgcctggga	(SEQ ID NO:18)
3702259	ttcggctggggccccccaccactgcctgggc	(SEQ ID NO:19)
SSU65940	ttcggtcacggcgtccacaagtgtcctggc	(SEQ ID NO:20)
STMOLEP	ttcgggcacggagcgcaccactgcatcggc	(SEQ ID NO:21)
SERCP450A	ttcggccacggcatccacttctgcgtgggc	(SEQ ID NO:22)

FIG. 2

```
EPO-B     MTDVEETTATLPLARKCPFSPP--PEYERLRRESPVSRVGLPSGQTAWALTRLEDIREML
1JINA     --------ATVPDLESDSFHVDWYSTYAELRETAPVTPVRFL-GQDAWLVTGYDEAKAAL
                  **:*  .. .*     . * .**. :**: * :  ** ** :*  :: :  *

EPO-B     SSPHFSSD--RQSPSFPLMVARQI--RREDKP-FRPSLIAMDPPEHGKARRDVVGEFTVK
1JINA     SDLRLSSDPKKKYPGVEVEFPAYLGFPEDVRNYFATNMGTSDPPTHTRLRKLVSQEFTVR
          *. ::***  :: *.. : ..  :   .: :  * ..: : *** * : *: *  ****:

EPO-B     RMKALQPRIQQIVDEHIDALLAGPKPADLVQALSLPVPSLVICELLGVPYSDHEFFQSCS
1JINA     RVEAMRPRVEQITAELLDEV-GDSGVVDIVDRFAHPLPIKVICELLGVDEAARGAFGRWS
          *::*::**::**. * :* : ...  .*:*: :: *:*  ******** : :  *   *

EPO-B     SRMLSREVT-AEERMTAFESLENYLDELVTKKEANATEDDLLGRQILKQRESGEADHGEL
1JINA     SEILVMDPERAEQRGQAAREVVNFILDLVERRRTEPGDDLLSALISVQDDDDGRLSADEL
          *.:*  :   **:*  * ..: *:: :** ::.::. :* * .   ::: :.*. . .**

EPO-B     VGLAFLLLIAGHETTANMISLGTVTLLENPDQLAKIKADPGKTLAAIEELLRIFTIAETA
1JINA     TSIALVLLLAGFEASVSLIGIGTYLLLTHPDQLALVRADPSALPNAVEEILRYIAPPETT
          ..:*::**:**.*::..:*.:**  ** :***** ::***.    *:**:** :: .**:

EPO-B     TSRFATADVEIGGTLIRAGEGVVGLSNAGNHDPDGFENPDTFDIERGARHHVAFGFGVHQ
1JINA     T-RFAAEEVEIGGVAIPQYSTVLVANGAANRDPSQFPDPHRFDVTRDTRGHLSFGQGIHF
          * ***: :*****. *   . *:  ..*.*:**. * :*. **: *.:* *::** *:*

EPO-B     CLGQNLARLELQIVFDTLFRRVPGIRIAVPVDELPFKHDSTIYGLHALPVTW--
1JINA     CMGRPLAKLEGEVALRALFGRFPALSLGIDADDVVWRRSLLLRGIDHLPVRLDG
          *:*: **:** ::.: :** *.*.: :.: .*:: :::.  : *:. ***
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FIG. 3

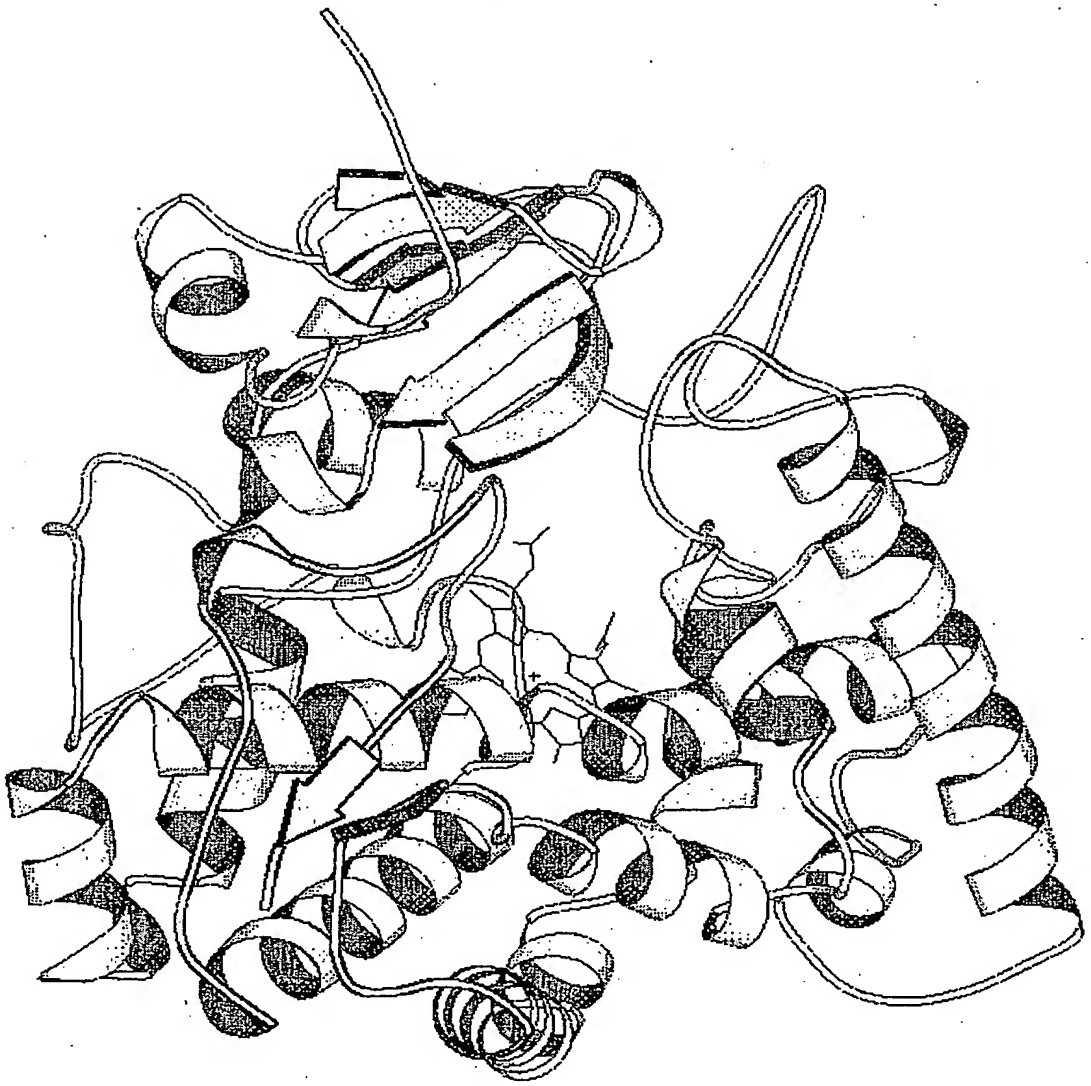

FIG. 4

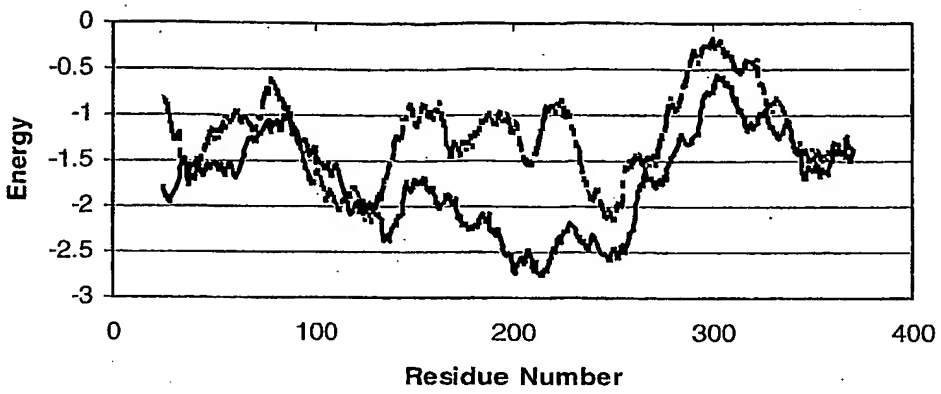

FIG. 5

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atcgcggggc acgagactac ggcgaacatg atctcgctcg gcacggtgac cctgctggag 780

aaccccgatc agctggcgaa gatcaaggcg gatccgggca agaccctcgc cgcgatcgag 840

gaactcctgc ggatcttcac catcgcggag acggcgaccc cacgcttcgc cacggcggac 900

gtcgagatcg gcggcacgct catccgcgcg ggtgaaggcg tcgtcggcct gagcaacgcg 960

ggcaaccacg atccggacgg cttcgagaac ccggacacct tcgacatcga acgcggcgcg 1020

cggcatcacg tcgccttcgg attcggtgtg caccaatgcc tcggccagaa cttggcgagg 1080

ttggaactcc agatcgtgtt cgataccctg ttccggcgag tgccgggcat ccggatcgcc 1140

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ccggtcacct ggtag 1215

<210> 31
<211> 404

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic

<400> 31

Met Thr Asp Val Glu Glu Thr Thr Ala Thr Leu Pro Leu Ala Arg Lys
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Cys Pro Phe Ser Pro Pro Pro Glu Tyr Glu Arg Leu Arg Arg Glu Ser
20 25 30

Pro Val Ser Arg Val Gly Leu Pro Ser Gly Gln Thr Ala Trp Ala Leu
35 40 45

Thr Arg Leu Glu Asp Ile Arg Glu Met Leu Ser Ser Pro His Phe Ser
50 55 60

Ser Asp Arg Gln Ser Pro Ser Phe Pro Leu Met Val Ala Arg Gln Ile
65 70 75 80

Arg Arg Glu Asp Lys Pro Phe Arg Pro Ser Leu Ile Ala Met Asp Pro
85 90 95

Pro Glu His Gly Lys Ala Arg Arg Asp Val Val Gly Glu Phe Thr Val
100 105 110

Lys Arg Met Lys Ala Leu Gln Pro Arg Ile Gln Gln Ile Val Asp Glu
115 120 125

His Ile Asp Ala Leu Leu Ala Gly Pro Lys Pro Ala Asp Leu Val Gln
130 135 140

Ala Leu Ser Leu Pro Val Pro Ser Leu Val Ile Cys Glu Leu Leu Gly
145 150 155 160

Val Pro Tyr Ser Asp His Glu Phe Phe Gln Ser Cys Ser Ser Arg Met
165 170 175

Leu Ser Arg Glu Val Thr Ala Glu Glu Arg Met Thr Ala Phe Glu Ser
180 185 190

Leu Glu Ser Tyr Leu Asp Glu Leu Val Thr Lys Lys Glu Ala Asn Ala

195 200 205

Thr Glu Asp Asp Leu Leu Gly Arg Gln Ile Leu Lys Gln Arg Glu Ser
210 215 220

Gly Glu Ala Asp His Gly Glu Leu Val Gly Leu Ala Phe Leu Leu Leu
225 230 235 240

Ile Ala Gly His Glu Thr Thr Ala Asn Met Ile Ser Leu Gly Thr Val
245 250 255

Thr Leu Leu Glu Asn Pro Asp Gln Leu Ala Lys Ile Lys Ala Asp Pro
260 265 270

Gly Lys Thr Leu Ala Ala Ile Glu Glu Leu Leu Arg Ile Phe Thr Ile
275 280 285

Ala Glu Thr Ala Thr Pro Arg Phe Ala Thr Ala Asp Val Glu Ile Gly
290 295 300

Gly Thr Leu Ile Arg Ala Gly Glu Gly Val Val Gly Leu Ser Asn Ala
305 310 315 320

Gly Asn His Asp Pro Asp Gly Phe Glu Asn Pro Asp Thr Phe Asp Ile
325 330 335

Glu Arg Gly Ala Arg His His Val Ala Phe Gly Phe Gly Val His Gln
340 345 350

Cys Leu Gly Gln Asn Leu Ala Arg Leu Glu Leu Gln Ile Val Phe Asp
355 360 365

Thr Leu Phe Arg Arg Val Pro Gly Ile Arg Ile Ala Val Pro Val Asp
370 375 380

Glu Leu Pro Phe Lys His Asp Ser Thr Ile Tyr Gly Leu His Ala Leu
385 390 395 400

Pro Val Thr Trp

<210> 32
<211> 1215

<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic

<400> 32
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ccaccgcccg aatacgagcg gctccgccgg gaaagtccgg tttcccgggt cggtctcccc 120

tccggtcaaa ccgcttgggc gctcacccgg ctcgaagaca tccgcgaaat gctgagcagt 180

ccgcatttca gctccgaccg gcagagtccg tcgttcccgc tgatggtggc gcggcagatc 240

cggcgcgagg acaagccgtt ccgcccgtcc ctcatcgcga tggacccgcc ggaacacggc 300

aaggccaggc gtgacgtcgt cggggaattc accgtcaagc gcatgaaagc gcttcagcca 360

cgtattcagc agatcgtcga cgagcatatc gacgccctgc tcgccggccc caaacccgcc 420

gatctcgtcc aggcgctttc cctgccggtt ccgtccttgg tgatctgcga actgctcggt 480

gtcccctatt cggaccacga gttcttccag tcctgcagtt cccggatgct cagccgggaa 540

gtcaccgccg aagaacggat gaccgcgtac gagtcgctcg agaactatct cgacgaactc 600

gtcacgaaga aggaggcgaa cgccaccgag gacgacctcc tcggccgcca gatcctgaag 660

cagcgcgaat ccggcgaagc cgaccacggc cgcctggtcg gtctggcgtt cctcctgctc 720

atcgcggggc acgagactac ggcgaacatg atctcgctcg gcacggtgac cctgctggag 780

aaccccgatc agctggcgaa gatcaaggcg gatccgggca agaccctcgc cgcgatcgag 840

gaactcctgc ggatcttcac catcgcggag acggcgacct cacgcttcgc cacggcggac 900

gtcgagatcg gcggcacgct catccgcgcg ggtgaaggcg tcgtcggcct gagcaacgcg 960

ggcaaccacg atccggacgg cttcgagaac ccggacacct tcgacatcga acgcggcgcg 1020

cggcatcacg tcgccttcgg attcggtgtg caccaatgcc tcggccagaa cttggcgagg 1080

ttggaactcc agatcgtgtt cgatacgttg ttccggcgag tgccgggcat ccggatcgcc 1140

gtaccggtcg acgaactgcc gttcaagcac gattcgacga tctacggcct ccacgccctg 1200

ccggtcacct ggtag 1215

<210> 33
<211> 404
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic

<400> 33

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Met Thr Asp Val Glu Glu Thr Thr Ala Thr Leu Pro Leu Ala Arg Lys
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Cys Pro Phe Ser Pro Pro Pro Glu Tyr Glu Arg Leu Arg Arg Glu Ser
            20                  25                  30

Pro Val Ser Arg Val Gly Leu Pro Ser Gly Gln Thr Ala Trp Ala Leu
        35                  40                  45

Thr Arg Leu Glu Asp Ile Arg Glu Met Leu Ser Ser Pro His Phe Ser
    50                  55                  60

Ser Asp Arg Gln Ser Pro Ser Phe Pro Leu Met Val Ala Arg Gln Ile
65                  70                  75                  80

Arg Arg Glu Asp Lys Pro Phe Arg Pro Ser Leu Ile Ala Met Asp Pro
                85                  90                  95

Pro Glu His Gly Lys Ala Arg Arg Asp Val Val Gly Glu Phe Thr Val
            100                 105                 110

Lys Arg Met Lys Ala Leu Gln Pro Arg Ile Gln Gln Ile Val Asp Glu
        115                 120                 125

His Ile Asp Ala Leu Leu Ala Gly Pro Lys Pro Ala Asp Leu Val Gln
    130                 135                 140

Ala Leu Ser Leu Pro Val Pro Ser Leu Val Ile Cys Glu Leu Leu Gly
145                 150                 155                 160

Val Pro Tyr Ser Asp His Glu Phe Phe Gln Ser Cys Ser Ser Arg Met
                165                 170                 175

Leu Ser Arg Glu Val Thr Ala Glu Glu Arg Met Thr Ala Tyr Glu Ser
            180                 185                 190

Leu Glu Asn Tyr Leu Asp Glu Leu Val Thr Lys Lys Glu Ala Asn Ala
        195                 200                 205

Thr Glu Asp Asp Leu Leu Gly Arg Gln Ile Leu Lys Gln Arg Glu Ser
    210                 215                 220
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Gly Glu Ala Asp His Gly Arg Leu Val Gly Leu Ala Phe Leu Leu Leu
225 230 235 240

Ile Ala Gly His Glu Thr Thr Ala Asn Met Ile Ser Leu Gly Thr Val
245 250 255

Thr Leu Leu Glu Asn Pro Asp Gln Leu Ala Lys Ile Lys Ala Asp Pro
260 265 270

Gly Lys Thr Leu Ala Ala Ile Glu Glu Leu Leu Arg Ile Phe Thr Ile
275 280 285

Ala Glu Thr Ala Thr Ser Arg Phe Ala Thr Ala Asp Val Glu Ile Gly
290 295 300

Gly Thr Leu Ile Arg Ala Gly Glu Gly Val Val Gly Leu Ser Asn Ala
305 310 315 320

Gly Asn His Asp Pro Asp Gly Phe Glu Asn Pro Asp Thr Phe Asp Ile
325 330 335

Glu Arg Gly Ala Arg His His Val Ala Phe Gly Phe Gly Val His Gln
340 345 350

Cys Leu Gly Gln Asn Leu Ala Arg Leu Glu Leu Gln Ile Val Phe Asp
355 360 365

Thr Leu Phe Arg Arg Val Pro Gly Ile Arg Ile Ala Val Pro Val Asp
370 375 380

Glu Leu Pro Phe Lys His Asp Ser Thr Ile Tyr Gly Leu His Ala Leu
385 390 395 400

Pro Val Thr Trp

<210> 34
<211> 1215
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic

<400> 34
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tccggtcaaa ccgcttgggc gctcacccgg ctcgaagaca tccgcgaaat gctgagcagt 180

ccgcatttca gctccgaccg gcagagtccg tcgttcccgc tgatggtggc gcggcagatc 240

cggcgcgagg acaagccgtt ccgcccgtcc ctcgtcgcga tggacccgcc ggaacacggc 300

aaggccaggc gtgacgtcgt cggggaattc accgtcaagc gcatgaaagc gcttcagcca 360

cgtattcagc agatcgtcga cgagcatatc gacgccctgc tcgccggccc caaacccgcc 420

gatctcgtcc aggcgctttc cctgccggtt ccgtccttgg tgatctgcga actgctcggt 480

gtcccctatt cggaccacga gttcttccag tcctgcagtt cccggatgct cagccgggaa 540

gtcaccgccg aagaacggat gaccgcgttc gagtcgctcg agaactatct cgacgaactc 600

gtcacgaaga aggaggcgaa cgccaccgag gacgacctcc tcggccgcca gatcctgaag 660

cagcgcgaat ccggcgaagc cgaccacggc gaactggtcg gtctggcggc gctcctgctc 720

atcgcggggc acgagactac ggcgaacatg atctcgctcg gcacggtgac cctgctggag 780

aaccccgatc agctggcgaa gatcaaggcg gatccgggca agaccctcgc cgcgatcgag 840

gaactcctgc ggatcttcac catcgcggag acggcgacct cacgcttcgc cacggcggac 900

gtcgagatcg gcggcacgct catccgcgcg ggtgaaggcg tcgtcggcct gagcaacgcg 960

ggcaaccacg atccggacgg cttcgagaac ccggacacct tcgacatcga acgcggcgcg 1020

cggcatcacg tcgccttcgg attcggtgtg caccaatgcc tcggccagaa cttggcgagg 1080

ttggaactcc agatcgtgtt cgatacgttg ttccggcgag tgccgggcat ccggatcgcc 1140

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ccggtcacct ggtag 1215

<210> 35
<211> 404
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic

<400> 35

Met Thr Asp Val Glu Glu Thr Thr Ala Thr Leu Pro Leu Ala Arg Lys
1 5 10 15

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Cys Pro Phe Ser Pro Pro Pro Glu Tyr Glu Arg Leu Arg Arg Glu Ser
            20                  25                  30

Pro Val Ser Arg Val Gly Leu Pro Ser Gly Gln Thr Ala Trp Ala Leu
        35                  40                  45

Thr Arg Leu Glu Asp Ile Arg Glu Met Leu Ser Ser Pro His Phe Ser
    50                  55                  60

Ser Asp Arg Gln Ser Pro Ser Phe Pro Leu Met Val Ala Arg Gln Ile
65                  70                  75                  80

Arg Arg Glu Asp Lys Pro Phe Arg Pro Ser Leu Val Ala Met Asp Pro
                85                  90                  95

Pro Glu His Gly Lys Ala Arg Arg Asp Val Val Gly Glu Phe Thr Val
            100                 105                 110

Lys Arg Met Lys Ala Leu Gln Pro Arg Ile Gln Gln Ile Val Asp Glu
        115                 120                 125

His Ile Asp Ala Leu Leu Ala Gly Pro Lys Pro Ala Asp Leu Val Gln
    130                 135                 140

Ala Leu Ser Leu Pro Val Pro Ser Leu Val Ile Cys Glu Leu Leu Gly
145                 150                 155                 160

Val Pro Tyr Ser Asp His Glu Phe Phe Gln Ser Cys Ser Ser Arg Met
                165                 170                 175

Leu Ser Arg Glu Val Thr Ala Glu Glu Arg Met Thr Ala Phe Glu Ser
            180                 185                 190

Leu Glu Asn Tyr Leu Asp Glu Leu Val Thr Lys Lys Glu Ala Asn Ala
        195                 200                 205

Thr Glu Asp Asp Leu Leu Gly Arg Gln Ile Leu Lys Gln Arg Glu Ser
    210                 215                 220

Gly Glu Ala Asp His Gly Glu Leu Val Gly Leu Ala Ala Leu Leu Leu
225                 230                 235                 240
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Ile Ala Gly His Glu Thr Thr Ala Asn Met Ile Ser Leu Gly Thr Val
245 250 255

Thr Leu Leu Glu Asn Pro Asp Gln Leu Ala Lys Ile Lys Ala Asp Pro
260 265 270

Gly Lys Thr Leu Ala Ala Ile Glu Glu Leu Leu Arg Ile Phe Thr Ile
275 280 285

Ala Glu Thr Ala Thr Ser Arg Phe Ala Thr Ala Asp Val Glu Ile Gly
290 295 300

Gly Thr Leu Ile Arg Ala Gly Glu Gly Val Val Gly Leu Ser Asn Ala
305 310 315 320

Gly Asn His Asp Pro Asp Gly Phe Glu Asn Pro Asp Thr Phe Asp Ile
325 330 335

Glu Arg Gly Ala Arg His His Val Ala Phe Gly Phe Gly Val His Gln
340 345 350

Cys Leu Gly Gln Asn Leu Ala Arg Leu Glu Leu Gln Ile Val Phe Asp
355 360 365

Thr Leu Phe Arg Arg Val Pro Gly Ile Arg Ile Ala Val Pro Val Asp
370 375 380

Glu Leu Pro Phe Lys His Asp Ser Thr Ile Tyr Gly Leu His Ala Leu
385 390 395 400

Pro Val Thr Trp

<210> 36
<211> 1104
<212> DNA
<213> Amycolatopsis orientalis

<400> 36
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cgccgggaaa gtccggtttc ccgggtcggt ctcccgtccg gtcaaaccgc ttgggcgctc 120

acccggctcg aggacatccg cgaaatgctg agcagtccgc atttcagctc cgaccggcag 180

agtccgtcgt tcccgctgat ggtggcccgg cagatccggc gcgaggacaa gccgttccgc 240

ccgtccctca tcgcgatgga cccgccggaa cacagcaagg ccaggcgtga cgtcgtcggg 300

gaattcaccg tcaagcgcat gaaagcgctt cagccgcgta ttcagcagat cgtcgacgag 360

catatcgacg ccatgctcgc cggccccaaa cccgccgatc tcgtccaggc gctttccctg 420

ccggttccgt ccttggtgat ctgcgaactg ctcggtgtcc cctattcgga ccacgagttc 480

ttccagtcct gcagttcccg gatgctcagc cgggaagtca ccgccgaaga acggatgacc 540

gcgttcgagt cgctcgagaa ctatctcgac gaactcgtca cgaagaagga ggcgaacgcc 600

accgaggacg acctcctcgg ccgccagatc ctgaagcagc gcgaaacggg cgaagccgac 660

cacggcgaac tcgtcgggct ggcgttcctg ctgctcatcg cgggacacga gacgacggcg 720

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aaggccgatc cgggcaagac cctcgccgcg atcgaggagc tcctgcgggt cttcaccatc 840

gcggagacgg cgacctcacg cttcgccacg gcggacgtcg agatcggcgg cacgctcatc 900

cgcgcgggtg aaggcgtcgt cggcctgagc aacgcgggca accacgatcc ggaaggcttc 960

gagaacccgg acgccttcga catcgaacgc ggcgcgcggc accacgtcgc cttcggattc 1020

ggtgtgcacc aatgcctcgg ccagaacttg gcgaggttgg aactccagat cgtgttcgat 1080

acgttgttcc ggcgagtgcc gggc 1104

<210> 37
<211> 1103
<212> DNA
<213> Amycolatopsis orientalis

<400> 37
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ccgggaaagt ccggtttccc gggtcggtct cccgtccggt caaacggctt gggcgctcac 120

ccggctcgaa gacatccgcg aaatgctgag cagcccgcat ttcagttccg accggcagag 180

cccgtcgttc ccgctgatgg tcgcgcggca gatccgccgc gaggacaagc cgttccgccc 240

ctccctcatc gcgatggatc cgccggaaca cagccgggcc aggcgtgacg tcgtcgggga 300

attcaccgtc aagcggatga aggcgctcca gccgcgaatt cagcagatcg tcgacgaaca 360

tctcgacgcc ctgctcgcgg gccccaaacc cgccgatctc gtccaggcgc tttccctgcc 420

cgttccctcg ctggtgatct gcgaactgct cggcgtcccc tattcggacc acgagttctt 480

ccagtcctgc agttccagga tgctcagccg ggaggtcacc gccgaagaac ggatgaccgc 540

gttcgagcag ctcgaaaact atctcgacga actggtcacc aagaaggagg cgaacgccac 600

cgaggacgac ctcctcggcc gtcagatcct gaaacagcgg gaaacgggcg aggccgacca 660

cggtgaactc gtcgggctgg cgttcctgct gctcatcgcc ggacacgaga ccacggcgaa 720

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ggtgcaccag tgtctcggcc agaacttggc gaggttggaa ctccagatcg tcttcgatac 1080

gttgttccgg cgagtgccgg gcc 1103

<210> 38
<211> 817
<212> DNA
<213> Amycolatopsis orientalis

<400> 38
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ccggatccgc cttgatcttc gccagctgat cggggttctc cagcagggtc accgtgccga 180

gcgagatcat gttcgccgta gtctcgtgcc ccgcgatgag caggaggaac gccagaccga 240

ccagttcgcc gtggtcggct tcgccggatt cgcgctgctt caggatctgg cggccgagga 300

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cgatgaggga cgggcggaac ggcttgtcct cgcgccggat ctgccgcgcc accatcagcg 720

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cttcgagccg ggtgagcgcc caagcggttt gaccgga 817

<210> 39

<211> 1105
<212> DNA
<213> Amycolatopsis orientalis

<400> 39
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tcacccggct cgaggacatc cgcgaaatgc tgagcagtcc gcatttcagc tccgaccggc 180

agagtccgtc gttcccgctg atggtggccc ggcagatccg gcgcgaggac aagccgttcc 240

gcccgtccct catctcgatg gacccgccgg aacacagcaa ggccaggcgt gacgtcgtcg 300

gggaattcac cgtcaagcgc atgaaagcgc ttcagccgcg tattcagcag atcgtcgacg 360

agcatatcga cgccctgctc gccggcccca aacccgccga tctcgtccag gcgctttccc 420

tgccggttcc gtccttggtg atctgcgaac tgctcggtgt cccctattcg gaccacgagt 480

tcttccagtc ctgcagttcc cggatgctca gccgggaagt caccgccgaa gaacggatga 540

ccgcgttcga gtcgctcgag aactatctcg acgaactcgt cacgaagaag gaggcgaacg 600

ccaccgagga cgacctcctc ggccgccaga tcctgaagca gcgcgaaacg ggcgaagccg 660

accacggcga actggtcggg ctggcgttcc tcctgctcat cgcgggacac gagacgacgg 720

cgaacatgat ctcgctcggc acggcgaccc tgctggagaa ccccgaccag ctggcgaaga 780

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tcggtgtgca ccaatgcctc ggccagaact tggcgaggtt ggaactccag atcgtgttcg 1080

atacgttgtt ccggcgagtg ccggg 1105

<210> 40
<211> 1304
<212> DNA
<213> Amycolatopsis orientalis

<400> 40
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gggaaagtcc ggtttcccgg gtcggtctcc cctccggtca aaccgcttgg gcgctcaccc 120

ggctcgaaga catccgcgaa atgctgagca gtccgcattt cagctccgac cggcagagtc 180

cgtcgttccc gctgatggtg gcgcggcaga tccggcgcga ggacaagccg ttccgcccgt 240

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ttccgtcctt ggtgatctgc gaactgctcg gtgtccccta ttcggaccac gagttcttcc 480

agtcctgcag ttcccggatg ctcagccggg aagtcaccgc cgaagaacgg atgaccgcgt 540

tcgagtcgct cgagaactat ctcgacgaac tcgtcacgaa gaaggaggcg aacgccaccg 600

aggacgacct cctcggccgc cagatcctga agcagcgcga atccggcgaa gccgaccacg 660

gcgaactggt cggtctggcg ttcctcctgc tcatcgcggg gcacgagact acggcgaaca 720

tgatctcgct cggcacggtg accctgctgg agaaccccga tcagctggcg aagatcaagg 780

cggatccggg caagaccctc gccgcgatcg aggaactcct gcggatcttc accatcgcgg 840

agacggcgac ctcacgcttc gccacggcgg acgtcgagat cggcggcacg ctcatccgcg 900

cgggtgaagg cgtcgtcggc ctgagcaacg cgggcaacca cgatccggac ggcttcgaga 960

acccggacac cttcgacatc gaacgcggcg cgcggcatca cgtcgccttc ggattcggtg 1020

tgcaccaatg cctcggccag aacttggcga ggttggaact ccagatcgtg ttcgatacgt 1080

tgttccggcg agtgccgggc atccggatcg ccgtaccggt cgacgaactg ccgttcaagc 1140

acgattcgac gatctacggc ctccgcgccc tgccggtcac ctggtaggag gagccatgaa 1200

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tctgttcgac cagagcgagg acgacgggac ggtcctcctg ctga 1304

<210> 41
<211> 825
<212> DNA
<213> Amycolatopsis orientalis

<400> 41
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ccggcgcgag gacaagccgt tccgcccgtc cctcatcgcg atggacccgc cggaacacag 180

caaggccagg cgtgacgtcg tcggggaatt caccgtcaag cgcatgaaag cgcttcagcc 240

gcgtattcag cagatcgtcg acgagcatat cgacgccctg ctcgccggcc ccaaacccgc 300

cgatctcgtc caggcgcttt ccctgccggt tccgtccttg gtgatctgcg aactgctcgg 360

tgtcccctat tcggaccacg agttcttcca gtcctgcagt tcccggatgc tcagccggga 420

agtcaccgcc gaagaacgga tgaccgcgtt cgagtcgctc gagaactatc tcgacgaact 480

cgtcacgaag aaggaggcga acgccaccga ggacgacctc ctcggccgcc agatcctgaa 540

gcagcgggaa acgggcgagg ccgaccacgg cgaactcgtc gggctggcgt tcctgctgct 600

catcgccggg cacgagacga cggcgaacat gatctcgctc ggcacggcga ccctgctgga 660

gaaccccgac cagctggcga agatcaaggc ggatccgggc aagaccctcg ccgcgatcga 720

ggaactgctg cgcgtcttca cgatcgcgga gacggcgacc tcacgcttcg ccacggcgga 780

cgtcgagatc ggcggcacgc tcatccgcgc gggtgaaggc gtcgt 825

<210> 42
<211> 1103
<212> DNA
<213> Amycolatopsis orientalis

<400> 42
gcgaccttgc cactggcccg caaatgcccg ttttcaccac cgcccgaata cgagcggctc 60

cgccgggaaa gtccggtttc ccgggtcggt ctcccctccg gtcaaaccgc ttgggcgctc 120

acccggctcg aagacatccg cgaaatgctg agcagtccgc atttcagctc cgaccggcag 180

agtccgtcgt tcccgctgat ggtggcgcgg cagatccggc gcgaggacaa gccgttccgc 240

ccgtccctca tcgcgatgga cccgccggaa cacggcaagg ccaggcgtga cgtcgtcggg 300

gaattcaccg tcaagcgcat gaaagcgctt cagccacgta ttcagcagat cgtcgacgag 360

catatcgacg ccctgctcgc cggccccaaa cccgccgatc tcgtccaggc gctttccctg 420

ccggttccgt ccttggtgat ctgcgaactg ctcggtgtcc cctattcgga ccacgagttc 480

ttccagtcct gcagttcccg gatgctcagc cgggaagtca ccgccgaaga acggatgacc 540

gcgttcgagt cgctcgagaa ctatctcgac gaactcgtca cgaagaagga ggcgaacgcc 600

accgaggacg acctcctcgg ccgccagatc ctgaagcagc gcgaatccgg cgaagccgac 660

cacggcgaac tggtcggtct ggcgttcctc ctgctcatcg cggggcacga gactacggcg 720

aacatgatct cgctcggcac ggtgaccctg ctggagaacc ccgatcagct ggcgaagatc 780

aaggcggatc cgggcaagac cctcgccgcg atcgaggaac tcctgcggat cttcaccatc 840

gcggagacgg cgacctcacg cttcgccacg gcggacgtcg agatcggcgg cacgctcatc 900

cgcgcgggtg aaggcgtcgt cggcctgagc aacgcgggca accacgatcc ggacggcttc 960

gagaacccgg acaccttcga catcgaacgc ggcgcgcggc atcacgtcgc cttcggattc 1020

ggtgtgcacc aatgcctcgg ccagaacttg gcgaggttgg aactccagat cgtgttcgat 1080

acgttgttcc ggcgagtgcc ggg 1103

<210> 43
<211> 402
<212> PRT
<213> Amycolatopsis orientalis

<400> 43

Met Thr Asp Val Glu Glu Thr Thr Ala Thr Leu Pro Leu Ala Arg Lys
1 5 10 15

Cys Pro Phe Ser Pro Pro Pro Glu Tyr Glu Arg Leu Arg Arg Glu Ser
20 25 30

Pro Val Ser Arg Val Gly Leu Pro Ser Gly Gln Thr Ala Trp Ala Leu
35 40 45

Thr Arg Leu Glu Asp Ile Arg Glu Met Leu Ser Ser Pro His Phe Ser
50 55 60

Ser Asp Arg Gln Ser Pro Ser Phe Pro Leu Met Val Ala Arg Gln Ile
65 70 75 80

Arg Arg Glu Asp Lys Pro Phe Arg Pro Ser Leu Ile Ala Met Asp Pro
85 90 95

Pro Glu His Ser Lys Ala Arg Arg Asp Val Val Gly Glu Phe Thr Val
100 105 110

Lys Arg Met Lys Ala Leu Gln Pro Arg Ile Gln Gln Ile Val Asp Glu
115 120 125

His Ile Asp Ala Met Leu Ala Gly Pro Lys Pro Ala Asp Leu Val Gln
130 135 140

Ala Leu Ser Leu Pro Val Pro Ser Leu Val Ile Cys Glu Leu Leu Gly
145 150 155 160

Val Pro Tyr Ser Asp His Glu Phe Phe Gln Ser Cys Ser Ser Arg Met
165 170 175

Leu Ser Arg Glu Val Thr Ala Glu Glu Arg Met Thr Ala Phe Glu Ser
180 185 190

```
Leu Glu Asn Tyr Leu Asp Glu Leu Val Thr Lys Lys Glu Ala Asn Ala
        195                 200                 205

Thr Glu Asp Asp Leu Leu Gly Arg Gln Ile Leu Lys Gln Arg Glu Thr
    210                 215                 220

Gly Glu Ala Asp His Gly Glu Leu Val Gly Leu Ala Phe Leu Leu Leu
225                 230                 235                 240

Ile Ala Gly His Glu Thr Thr Ala Asn Met Ile Ser Leu Gly Thr Ala
                245                 250                 255

Thr Leu Leu Glu Asn Pro Asp Gln Leu Ala Lys Ile Lys Ala Asp Pro
            260                 265                 270

Gly Lys Thr Leu Ala Ala Ile Glu Glu Leu Leu Arg Val Phe Thr Ile
        275                 280                 285

Ala Glu Thr Ala Thr Ser Arg Phe Ala Thr Ala Asp Val Glu Ile Gly
    290                 295                 300

Gly Thr Leu Ile Arg Ala Gly Glu Gly Val Val Gly Leu Ser Asn Ala
305                 310                 315                 320

Gly Asn His Asp Pro Glu Gly Phe Glu Asn Pro Asp Ala Phe Asp Ile
                325                 330                 335

Glu Arg Gly Ala Arg His His Val Ala Phe Gly Phe Gly Val His Gln
            340                 345                 350

Cys Leu Gly Gln Asn Leu Ala Arg Leu Glu Leu Gln Ile Val Phe Asp
        355                 360                 365

Thr Leu Phe Arg Arg Val Pro Gly Ile Arg Ile Ala Val Pro Val Asp
    370                 375                 380

Glu Leu Pro Phe Lys His Asp Ser Thr Ile Tyr Gly Leu His Ala Leu
385                 390                 395                 400

Pro Val
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<210> 44
<211> 367
<212> PRT
<213> Amycolatopsis orientalis

<400> 44

Thr Leu Pro Leu Ala Arg Lys Cys Pro Phe Ser Pro Pro Pro Glu Tyr
1 5 10 15

Glu Arg Leu Arg Arg Glu Ser Pro Val Ser Arg Val Gly Leu Pro Ser
20 25 30

Gly Gln Thr Ala Trp Ala Leu Thr Arg Leu Glu Asp Ile Arg Glu Met
35 40 45

Leu Ser Ser Pro His Phe Ser Ser Asp Arg Gln Ser Pro Ser Phe Pro
50 55 60

Leu Met Val Ala Arg Gln Ile Arg Arg Glu Asp Lys Pro Phe Arg Pro
65 70 75 80

Ser Leu Ile Ala Met Asp Pro Pro Glu His Ser Arg Ala Arg Arg Asp
85 90 95

Val Val Gly Glu Phe Thr Val Lys Arg Met Lys Ala Leu Gln Pro Arg
100 105 110

Ile Gln Gln Ile Val Asp Glu His Leu Asp Ala Leu Leu Ala Gly Pro
115 120 125

Lys Pro Ala Asp Leu Val Gln Ala Leu Ser Leu Pro Val Pro Ser Leu
130 135 140

Val Ile Cys Glu Leu Leu Gly Val Pro Tyr Ser Asp His Glu Phe Phe
145 150 155 160

Gln Ser Cys Ser Ser Arg Met Leu Ser Arg Glu Val Thr Ala Glu Glu
165 170 175

Arg Met Thr Ala Phe Glu Gln Leu Glu Asn Tyr Leu Asp Glu Leu Val
180 185 190

Thr Lys Lys Glu Ala Asn Ala Thr Glu Asp Asp Leu Leu Gly Arg Gln

195 200 205

Ile Leu Lys Gln Arg Glu Thr Gly Glu Ala Asp His Gly Glu Leu Val
210 215 220

Gly Leu Ala Phe Leu Leu Leu Ile Ala Gly His Glu Thr Thr Ala Asn
225 230 235 240

Met Ile Ser Leu Gly Thr Val Thr Leu Leu Glu Asn Pro Asp Gln Leu
245 250 255

Ala Lys Ile Lys Ala Asp Pro Gly Lys Thr Leu Ala Ala Ile Glu Glu
260 265 270

Leu Leu Arg Val Phe Thr Ile Ala Glu Thr Ala Thr Ser Arg Phe Ala
275 280 285

Thr Ala Asp Val Glu Ile Gly Gly Thr Leu Ile Arg Ala Gly Glu Gly
290 295 300

Val Val Gly Leu Ser Asn Ala Gly Asn His Asp Pro Asp Gly Phe Glu
305 310 315 320

Asn Pro Asp Thr Phe Asp Ile Glu Arg Gly Ala Arg His His Val Ala
325 330 335

Phe Gly Phe Gly Val His Gln Cys Leu Gly Gln Asn Leu Ala Arg Leu
340 345 350

Glu Leu Gln Ile Val Phe Asp Thr Leu Phe Arg Arg Val Pro Gly
355 360 365

<210> 45
<211> 272
<212> PRT
<213> Amycolatopsis orientalis

<400> 45

Ser Gly Gln Thr Ala Trp Ala Leu Thr Arg Leu Glu Asp Ile Arg Glu
1 5 10 15

Met Leu Ser Ser Pro His Phe Ser Ser Asp Arg Gln Ser Pro Ser Phe
20 25 30

```
Pro Leu Met Val Ala Arg Gln Ile Arg Arg Glu Asp Lys Pro Phe Arg
        35                  40                  45

Pro Ser Leu Ile Ala Met Asp Pro Pro Glu His Gly Lys Ala Arg Arg
    50                  55                  60

Asp Val Val Gly Glu Phe Thr Val Lys Arg Met Lys Ala Leu Gln Pro
65                  70                  75                  80

Arg Ile Gln Gln Ile Val Asp Glu His Ile Asp Ala Leu Leu Ala Gly
                85                  90                  95

Pro Lys Pro Ala Asp Leu Val Gln Ala Leu Ser Leu Pro Val Pro Ser
            100                 105                 110

Leu Val Ile Cys Glu Leu Leu Gly Val Pro Tyr Ser Asp His Glu Phe
        115                 120                 125

Phe Gln Ser Cys Ser Ser Arg Met Leu Ser Arg Glu Val Thr Ala Glu
    130                 135                 140

Glu Arg Met Thr Ala Phe Glu Ser Leu Glu Asn Tyr Leu Asp Glu Leu
145                 150                 155                 160

Val Thr Lys Lys Glu Ala Asn Ala Thr Glu Asp Asp Leu Leu Gly Arg
                165                 170                 175

Gln Ile Leu Lys Gln Arg Glu Ser Gly Glu Ala Asp His Gly Glu Leu
            180                 185                 190

Val Gly Leu Ala Phe Leu Leu Leu Ile Ala Gly His Glu Thr Thr Ala
        195                 200                 205

Asn Met Ile Ser Leu Gly Thr Val Thr Leu Leu Glu Asn Pro Asp Gln
    210                 215                 220

Leu Ala Lys Ile Lys Ala Asp Pro Gly Lys Thr Leu Ala Ala Ile Glu
225                 230                 235                 240

Glu Leu Leu Arg Ile Phe Thr Ile Ala Glu Thr Ala Thr Ser Arg Phe
                245                 250                 255
```

Ala Thr Ala Asp Val Glu Ile Gly Gly Thr Leu Ile Arg Ala Gly Glu
260 265 270

<210> 46
<211> 367
<212> PRT
<213> Amycolatopsis orientalis

<400> 46

Ala Thr Leu Pro Leu Ala Arg Lys Cys Pro Phe Ser Pro Pro Pro Glu
1 5 10 15

Tyr Glu Arg Leu Arg Arg Glu Ser Pro Val Ser Arg Val Gly Leu Pro
20 25 30

Ser Gly Gln Thr Ala Trp Ala Leu Thr Arg Leu Glu Asp Ile Arg Glu
35 40 45

Met Leu Ser Ser Pro His Phe Ser Ser Asp Arg Gln Ser Pro Ser Phe
50 55 60

Pro Leu Met Val Ala Arg Gln Ile Arg Arg Glu Asp Lys Pro Phe Arg
65 70 75 80

Pro Ser Leu Ile Ser Met Asp Pro Pro Glu His Ser Lys Ala Arg Arg
85 90 95

Asp Val Val Gly Glu Phe Thr Val Lys Arg Met Lys Ala Leu Gln Pro
100 105 110

Arg Ile Gln Gln Ile Val Asp Glu His Ile Asp Ala Leu Leu Ala Gly
115 120 125

Pro Lys Pro Ala Asp Leu Val Gln Ala Leu Ser Leu Pro Val Pro Ser
130 135 140

Leu Val Ile Cys Glu Leu Leu Gly Val Pro Tyr Ser Asp His Glu Phe
145 150 155 160

Phe Gln Ser Cys Ser Ser Arg Met Leu Ser Arg Glu Val Thr Ala Glu
165 170 175

Glu Arg Met Thr Ala Phe Glu Ser Leu Glu Asn Tyr Leu Asp Glu Leu
180 185 190

Val Thr Lys Lys Glu Ala Asn Ala Thr Glu Asp Asp Leu Leu Gly Arg
195 200 205

Gln Ile Leu Lys Gln Arg Glu Thr Gly Glu Ala Asp His Gly Glu Leu
210 215 220

Val Gly Leu Ala Phe Leu Leu Leu Ile Ala Gly His Glu Thr Thr Ala
225 230 235 240

Asn Met Ile Ser Leu Gly Thr Ala Thr Leu Leu Glu Asn Pro Asp Gln
245 250 255

Leu Ala Lys Ile Lys Ala Asp Pro Gly Lys Thr Leu Ala Ala Ile Glu
260 265 270

Glu Leu Leu Arg Val Phe Thr Ile Ala Glu Thr Ala Thr Ser Arg Phe
275 280 285

Ala Thr Ala Asp Val Glu Ile Gly Gly Thr Leu Ile Arg Ala Gly Glu
290 295 300

Gly Val Val Gly Leu Ser Asn Ala Gly Asn His Asp Pro Glu Gly Phe
305 310 315 320

Glu Asn Pro Asp Ala Phe Asp Ile Glu Arg Gly Ala Arg His His Val
325 330 335

Ala Phe Gly Phe Gly Val His Gln Cys Leu Gly Gln Asn Leu Ala Arg
340 345 350

Leu Glu Leu Gln Ile Val Phe Asp Thr Leu Phe Arg Arg Val Pro
355 360 365

<210> 47
<211> 394
<212> PRT
<213> Amycolatopsis orientalis

<400> 47

Leu Pro Leu Ala Arg Lys Cys Pro Phe Ser Pro Pro Pro Glu Tyr Glu
1 5 10 15

```
Arg Leu Arg Arg Glu Ser Pro Val Ser Arg Val Gly Leu Pro Ser Gly
            20                  25                  30

Gln Thr Ala Trp Ala Leu Thr Arg Leu Glu Asp Ile Arg Glu Met Leu
        35                  40                  45

Ser Ser Pro His Phe Ser Ser Asp Arg Gln Ser Pro Ser Phe Pro Leu
    50                  55                  60

Met Val Ala Arg Gln Ile Arg Arg Glu Asp Lys Pro Phe Arg Pro Ser
65                  70                  75                  80

Leu Ile Ala Met Asp Pro Pro Glu His Gly Lys Ala Arg Arg Asp Val
                85                  90                  95

Val Gly Glu Phe Thr Val Lys Arg Met Lys Ala Leu Gln Pro Arg Ile
            100                 105                 110

Gln Gln Ile Val Asp Glu His Ile Asp Ala Leu Leu Ala Gly Pro Lys
        115                 120                 125

Pro Ala Asp Leu Val Gln Ala Leu Ser Leu Pro Val Pro Ser Leu Val
    130                 135                 140

Ile Cys Glu Leu Leu Gly Val Pro Tyr Ser Asp His Glu Phe Phe Gln
145                 150                 155                 160

Ser Cys Ser Ser Arg Met Leu Ser Arg Glu Val Thr Ala Glu Glu Arg
                165                 170                 175

Met Thr Ala Phe Glu Ser Leu Glu Asn Tyr Leu Asp Glu Leu Val Thr
            180                 185                 190

Lys Lys Glu Ala Asn Ala Thr Glu Asp Asp Leu Leu Gly Arg Gln Ile
        195                 200                 205

Leu Lys Gln Arg Glu Ser Gly Glu Ala Asp His Gly Glu Leu Val Gly
    210                 215                 220

Leu Ala Phe Leu Leu Leu Ile Ala Gly His Glu Thr Thr Ala Asn Met
225                 230                 235                 240

Ile Ser Leu Gly Thr Val Thr Leu Leu Glu Asn Pro Asp Gln Leu Ala
```

245 250 255

Lys Ile Lys Ala Asp Pro Gly Lys Thr Leu Ala Ala Ile Glu Glu Leu
260 265 270

Leu Arg Ile Phe Thr Ile Ala Glu Thr Ala Thr Ser Arg Phe Ala Thr
275 280 285

Ala Asp Val Glu Ile Gly Gly Thr Leu Ile Arg Ala Gly Glu Gly Val
290 295 300

Val Gly Leu Ser Asn Ala Gly Asn His Asp Pro Asp Gly Phe Glu Asn
305 310 315 320

Pro Asp Thr Phe Asp Ile Glu Arg Gly Ala Arg His His Val Ala Phe
325 330 335

Gly Ile Gly Val His Gln Cys Leu Gly Gln Asn Leu Ala Arg Leu Glu
340 345 350

Leu Gln Ile Val Phe Asp Thr Leu Phe Arg Arg Val Pro Gly Ile Arg
355 360 365

Ile Ala Val Pro Val Asp Glu Leu Pro Phe Lys His Asp Ser Thr Ile
370 375 380

Tyr Gly Leu Arg Ala Leu Pro Val Thr Trp
385 390

<210> 48
<211> 274
<212> PRT
<213> Amycolatopsis orientalis

<400> 48

Ser Gly Gln Thr Ala Trp Ala Leu Thr Arg Leu Glu Asp Ile Arg Glu
1 5 10 15

Met Leu Ser Ser Pro His Phe Ser Ser Asp Arg Gln Asn Pro Ser Phe
20 25 30

Pro Leu Met Val Ala Arg Gln Ile Arg Arg Glu Asp Lys Pro Phe Arg
35 40 45

```
Pro Ser Leu Ile Ala Met Asp Pro Pro Glu His Ser Lys Ala Arg Arg
    50                  55                  60

Asp Val Val Gly Glu Phe Thr Val Lys Arg Met Lys Ala Leu Gln Pro
65                  70                  75                  80

Arg Ile Gln Gln Ile Val Asp Glu His Ile Asp Ala Leu Leu Ala Gly
                85                  90                  95

Pro Lys Pro Ala Asp Leu Val Gln Ala Leu Ser Leu Pro Val Pro Ser
            100                 105                 110

Leu Val Ile Cys Glu Leu Leu Gly Val Pro Tyr Ser Asp His Glu Phe
        115                 120                 125

Phe Gln Ser Cys Ser Ser Arg Met Leu Ser Arg Glu Val Thr Ala Glu
    130                 135                 140

Glu Arg Met Thr Ala Phe Glu Ser Leu Glu Asn Tyr Leu Asp Glu Leu
145                 150                 155                 160

Val Thr Lys Lys Glu Ala Asn Ala Thr Glu Asp Asp Leu Leu Gly Arg
                165                 170                 175

Gln Ile Leu Lys Gln Arg Glu Thr Gly Glu Ala Asp His Gly Glu Leu
            180                 185                 190

Val Gly Leu Ala Phe Leu Leu Leu Ile Ala Gly His Glu Thr Thr Ala
        195                 200                 205

Asn Met Ile Ser Leu Gly Thr Ala Thr Leu Leu Glu Asn Pro Asp Gln
    210                 215                 220

Leu Ala Lys Ile Lys Ala Asp Pro Gly Lys Thr Leu Ala Ala Ile Glu
225                 230                 235                 240

Glu Leu Leu Arg Val Phe Thr Ile Ala Glu Thr Ala Thr Ser Arg Phe
                245                 250                 255

Ala Thr Ala Asp Val Glu Ile Gly Gly Thr Leu Ile Arg Ala Gly Glu
            260                 265                 270
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Gly Val

<210> 49
<211> 367
<212> PRT
<213> Amycolatopsis orientalis

<400> 49

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Ala Thr Leu Pro Leu Ala Arg Lys Cys Pro Phe Ser Pro Pro Pro Glu
1               5                  10                  15

Tyr Glu Arg Leu Arg Arg Glu Ser Pro Val Ser Arg Val Gly Leu Pro
            20                  25                  30

Ser Gly Gln Thr Ala Trp Ala Leu Thr Arg Leu Glu Asp Ile Arg Glu
        35                  40                  45

Met Leu Ser Ser Pro His Phe Ser Ser Asp Arg Gln Ser Pro Ser Phe
    50                  55                  60

Pro Leu Met Val Ala Arg Gln Ile Arg Arg Glu Asp Lys Pro Phe Arg
65                  70                  75                  80

Pro Ser Leu Ile Ala Met Asp Pro Pro Glu His Gly Lys Ala Arg Arg
                85                  90                  95

Asp Val Val Gly Glu Phe Thr Val Lys Arg Met Lys Ala Leu Gln Pro
            100                 105                 110

Arg Ile Gln Gln Ile Val Asp Glu His Ile Asp Ala Leu Leu Ala Gly
        115                 120                 125

Pro Lys Pro Ala Asp Leu Val Gln Ala Leu Ser Leu Pro Val Pro Ser
    130                 135                 140

Leu Val Ile Cys Glu Leu Leu Gly Val Pro Tyr Ser Asp His Glu Phe
145                 150                 155                 160

Phe Gln Ser Cys Ser Ser Arg Met Leu Ser Arg Glu Val Thr Ala Glu
                165                 170                 175

Glu Arg Met Thr Ala Phe Glu Ser Leu Glu Asn Tyr Leu Asp Glu Leu
            180                 185                 190
```

Val Thr Lys Lys Glu Ala Asn Ala Thr Glu Asp Asp Leu Leu Gly Arg
195 200 205

Gln Ile Leu Lys Gln Arg Glu Ser Gly Glu Ala Asp His Gly Glu Leu
210 215 220

Val Gly Leu Ala Phe Leu Leu Leu Ile Ala Gly His Glu Thr Thr Ala
225 230 235 240

Asn Met Ile Ser Leu Gly Thr Val Thr Leu Leu Glu Asn Pro Asp Gln
245 250 255

Leu Ala Lys Ile Lys Ala Asp Pro Gly Lys Thr Leu Ala Ala Ile Glu
260 265 270

Glu Leu Leu Arg Ile Phe Thr Ile Ala Glu Thr Ala Thr Ser Arg Phe
275 280 285

Ala Thr Ala Asp Val Glu Ile Gly Gly Thr Leu Ile Arg Ala Gly Glu
290 295 300

Gly Val Val Gly Leu Ser Asn Ala Gly Asn His Asp Pro Asp Gly Phe
305 310 315 320

Glu Asn Pro Asp Thr Phe Asp Ile Glu Arg Gly Ala Arg His His Val
325 330 335

Ala Phe Gly Phe Gly Val His Gln Cys Leu Gly Gln Asn Leu Ala Arg
340 345 350

Leu Glu Leu Gln Ile Val Phe Asp Thr Leu Phe Arg Arg Val Pro
355 360 365

<210> 50
<211> 25
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic

<400> 50
aggaaaccac cgcgaccttg ccact 25

<210> 51
<211> 25
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic

<400> 51
accgaatccg aaggcgacgt gatgc 25

<210> 52
<211> 23
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic

<400> 52
cggaatgaat ccatccgcat acg 23

<210> 53
<211> 23
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic

<400> 53
tgatcttcat ggctcctcct acc 23

<210> 54
<211> 35
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (18)..(20)
<223> n=a, c, g or t

<400> 54
gcgaagccga ccacggcnnn ctggtcggtc tggcg 35

<210> 55
<211> 35

<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (16)..(18)
<223> n=a, c, g or t

<400> 55
cgccagaccg accagnnngc cgtggtcggc ttcgc 35

<210> 56
<211> 35
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (14)..(14)
<223> n=a, c, g or t

<400> 56
ggtcggtctg gcgnysctcc tgctcatcgc ggggc 35

<210> 57
<211> 35
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (22)..(22)
<223> n=a, c, g or t

<400> 57
gccccgcgat gagcaggags rncgccagac cgacc 35

<210> 58
<211> 35
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (17)..(17)
<223> n=a, c, g or t

<400> 58
ggtcggtctg gcgttcnysc tgctcatcgc ggggc 35

<210> 59
<211> 35
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (19)..(19)
<223> n=a, c, g or t

<400> 59
gccccgcgat gagcagsrng aacgccagac cgacc 35

<210> 60
<211> 1215
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic

<400> 60
atgaccgacg tcgaggaaac caccgcgacc ttgccactgg cccgcaaatg cccgttttca 60

ccaccgcccg aatacgagcg gctccgccgg gaaagtccgg tttcccgggt cggtctcccc 120

tccggtcaaa ccgcttgggc gctcacccgg ctcgaagaca tccgcgaaat gctgagcagt 180

ccgcatttca gctccgacca gcagagtccg tcgttcccgc tgatggtggc gcggcagatc 240

cggcgcgagg acaagccgtt ccgcccgtcc ctcgtcgcga tggacccgcc ggaacacggc 300

aaggccaggc gtgacgtcgt cggggaattc accgtcaagc gcatgaaagc gcttcagcca 360

cgtattcagc agatcgtcga cgagcatatc gacgccctgc tcgccggccc caaacccgcc 420

gatctcgtcc aggcgctttc cctgccggtt ccgtccttgg tgatctgcga actgctcggt 480

gtcccctatt cggaccacga gttcttccag tcctgcagtt cccggatgct cagccgggaa 540

gtcaccgccg aagaacggat gaccgcgttc gagtcgctcg agaactatct cgacgaactc 600

gtcacgaaga aggaggcgaa cgccaccgag gacgacctcc tcggccgcca gatcctgaag 660

cagcgcgaat ccggcgaagc cgaccacggc gaactggtcg gtctggcggc gctcctgctc 720

atcgcggggc acgagactac ggcgaacatg atctcgctcg gcacggtgac cctgctggag 780

aaccccgatc agctggcgaa gatcaaggcg gatccgggca agaccctcgc cgcgatcgag 840

gaactcctgc ggatcttcac catcgcggag acggcgacct cacgcttcgc cacggcggac 900

gtcgagatcg gcggcacgct catccgcgcg ggtgaaggcg tcgtcggcct gagcaacgcg 960

ggcaaccacg atccggacgg cttcgagaac ccggacacct tcgacatcga acgcggcgcg 1020

cggcatcacg tcgccttcgg attcggtgtg caccaatgcc tcggccagaa cttggcgagg 1080

ttggaactcc agatcgtgtt cgatacgttg ttccggcgag tgccgggcat ccggatcgcc 1140

gtaccggtcg acgaactgcc gttcaagcac gattcgacga tctacggcct ccacgccctg 1200

ccggtcacct ggtag 1215

<210> 61
<211> 404
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic

<400> 61

Met Thr Asp Val Glu Glu Thr Thr Ala Thr Leu Pro Leu Ala Arg Lys
1 5 10 15

Cys Pro Phe Ser Pro Pro Pro Glu Tyr Glu Arg Leu Arg Arg Glu Ser
20 25 30

Pro Val Ser Arg Val Gly Leu Pro Ser Gly Gln Thr Ala Trp Ala Leu
35 40 45

Thr Arg Leu Glu Asp Ile Arg Glu Met Leu Ser Ser Pro His Phe Ser
50 55 60

Ser Asp Gln Gln Ser Pro Ser Phe Pro Leu Met Val Ala Arg Gln Ile
65 70 75 80

Arg Arg Glu Asp Lys Pro Phe Arg Pro Ser Leu Val Ala Met Asp Pro

85 90 95

Pro Glu His Gly Lys Ala Arg Arg Asp Val Val Gly Glu Phe Thr Val
100 105 110

Lys Arg Met Lys Ala Leu Gln Pro Arg Ile Gln Gln Ile Val Asp Glu
115 120 125

His Ile Asp Ala Leu Leu Ala Gly Pro Lys Pro Ala Asp Leu Val Gln
130 135 140

Ala Leu Ser Leu Pro Val Pro Ser Leu Val Ile Cys Glu Leu Leu Gly
145 150 155 160

Val Pro Tyr Ser Asp His Glu Phe Phe Gln Ser Cys Ser Ser Arg Met
165 170 175

Leu Ser Arg Glu Val Thr Ala Glu Glu Arg Met Thr Ala Phe Glu Ser
180 185 190

Leu Glu Asn Tyr Leu Asp Glu Leu Val Thr Lys Lys Glu Ala Asn Ala
195 200 205

Thr Glu Asp Asp Leu Leu Gly Arg Gln Ile Leu Lys Gln Arg Glu Ser
210 215 220

Gly Glu Ala Asp His Gly Glu Leu Val Gly Leu Ala Ala Leu Leu Leu
225 230 235 240

Ile Ala Gly His Glu Thr Thr Ala Asn Met Ile Ser Leu Gly Thr Val
245 250 255

Thr Leu Leu Glu Asn Pro Asp Gln Leu Ala Lys Ile Lys Ala Asp Pro
260 265 270

Gly Lys Thr Leu Ala Ala Ile Glu Glu Leu Leu Arg Ile Phe Thr Ile
275 280 285

Ala Glu Thr Ala Thr Ser Arg Phe Ala Thr Ala Asp Val Glu Ile Gly
290 295 300

Gly Thr Leu Ile Arg Ala Gly Glu Gly Val Val Gly Leu Ser Asn Ala
305 310 315 320

Gly Asn His Asp Pro Asp Gly Phe Glu Asn Pro Asp Thr Phe Asp Ile
325 330 335

Glu Arg Gly Ala Arg His His Val Ala Phe Gly Phe Gly Val His Gln
340 345 350

Cys Leu Gly Gln Asn Leu Ala Arg Leu Glu Leu Gln Ile Val Phe Asp
355 360 365

Thr Leu Phe Arg Arg Val Pro Gly Ile Arg Ile Ala Val Pro Val Asp
370 375 380

Glu Leu Pro Phe Lys His Asp Ser Thr Ile Tyr Gly Leu His Ala Leu
385 390 395 400

Pro Val Thr Trp

<210> 62
<211> 1215
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic

<400> 62
atgaccgacg tcgaggaaac caccgcgacc ttgccactgg cccgcaaatg cccgttttca 60

ccaccgcccg aatacgagcg gctccgccgg gaaagtccgg tttcccgggt cggtctcccc 120

tccggtcaaa ccgcttgggc gctcacccgg ctcgaagaca tccgcgaaat gctgagcagt 180

ccgcatttca gctccgaccg gcagagtccg tcgttcccgc tgatggtggc gcggcagatc 240

cggcgcgagg acaagccgtt ccgcccgtcc ctcgtcggga tggacccgcc ggaacacggc 300

aaggccaggc gtgacgtcgt cggggaattc accgtcaagc gcatgaaagc gcttcagcca 360

cgtattcagc agatcgtcga cgagcatatc gacgccctgc tcgccggccc caaacccgcc 420

gatctcgtcc aggcgctttc cctgccggtt ccgtccttgg tgatctgcga actgctcggt 480

gtcccctatt cggaccacga gttcttccag tcctgcagtt cccggatgct cagccgggaa 540

gtcaccgccg aagaacggat gaccgcgttc gagtcgctcg agaactatct cgacgaactc 600

gtcacgaaga aggaggcgaa cgccaccgag gacgacctcc tcggccgcca gatcctgaag 660

cagcgcgaat ccggcgaagc cgaccacggc gaactggtcg gtctggcggc gctcctgctc 720

atcgcggggc acgagactac ggcgaacatg atctcgctcg gcacggtgac cctgctggag 780

aaccccgatc agctggcgaa gatcaaggcg gatccgggca agaccctcgc cgcgatcgag 840

gaactcctgc ggatcttcac catcgcggag acggcgacct cacgcttcgc cacggcggac 900

gtcgagatcg gcggcacgct catccgcgcg ggtgaaggcg tcgtcggcct gagcaacgcg 960

ggcaaccacg atccggacgg cttcgagaac ccggacacct tcgacatcga acgcggcgcg 1020

cggcatcacg tcgccttcgg attcggtgtg caccaatgcc tcggccagaa cttggcgagg 1080

ttggaactcc agaccgtgtt cgatacgttg ttccggcgag tgccgggcat ccggatcgcc 1140

gtaccggtcg acgaactgcc gttcaagcac gattcgacga tctacggcct ccacgccctg 1200

ccggtcacct ggtag 1215

<210> 63
<211> 404
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic

<400> 63

Met Thr Asp Val Glu Glu Thr Thr Ala Thr Leu Pro Leu Ala Arg Lys
1 5 10 15

Cys Pro Phe Ser Pro Pro Pro Glu Tyr Glu Arg Leu Arg Arg Glu Ser
20 25 30

Pro Val Ser Arg Val Gly Leu Pro Ser Gly Gln Thr Ala Trp Ala Leu
35 40 45

Thr Arg Leu Glu Asp Ile Arg Glu Met Leu Ser Ser Pro His Phe Ser
50 55 60

Ser Asp Arg Gln Ser Pro Ser Phe Pro Leu Met Val Ala Arg Gln Ile
65 70 75 80

Arg Arg Glu Asp Lys Pro Phe Arg Pro Ser Leu Val Gly Met Asp Pro
85 90 95

Pro Glu His Gly Lys Ala Arg Arg Asp Val Val Gly Glu Phe Thr Val
100 105 110

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Lys Arg Met Lys Ala Leu Gln Pro Arg Ile Gln Gln Ile Val Asp Glu
        115                 120                 125

His Ile Asp Ala Leu Leu Ala Gly Pro Lys Pro Ala Asp Leu Val Gln
    130                 135                 140

Ala Leu Ser Leu Pro Val Pro Ser Leu Val Ile Cys Glu Leu Leu Gly
145                 150                 155                 160

Val Pro Tyr Ser Asp His Glu Phe Phe Gln Ser Cys Ser Ser Arg Met
                165                 170                 175

Leu Ser Arg Glu Val Thr Ala Glu Glu Arg Met Thr Ala Phe Glu Ser
            180                 185                 190

Leu Glu Asn Tyr Leu Asp Glu Leu Val Thr Lys Lys Glu Ala Asn Ala
        195                 200                 205

Thr Glu Asp Asp Leu Leu Gly Arg Gln Ile Leu Lys Gln Arg Glu Ser
    210                 215                 220

Gly Glu Ala Asp His Gly Glu Leu Val Gly Leu Ala Ala Leu Leu Leu
225                 230                 235                 240

Ile Ala Gly His Glu Thr Thr Ala Asn Met Ile Ser Leu Gly Thr Val
                245                 250                 255

Thr Leu Leu Glu Asn Pro Asp Gln Leu Ala Lys Ile Lys Ala Asp Pro
            260                 265                 270

Gly Lys Thr Leu Ala Ala Ile Glu Glu Leu Leu Arg Ile Phe Thr Ile
        275                 280                 285

Ala Glu Thr Ala Thr Ser Arg Phe Ala Thr Ala Asp Val Glu Ile Gly
    290                 295                 300

Gly Thr Leu Ile Arg Ala Gly Glu Gly Val Val Gly Leu Ser Asn Ala
305                 310                 315                 320

Gly Asn His Asp Pro Asp Gly Phe Glu Asn Pro Asp Thr Phe Asp Ile
                325                 330                 335
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Glu Arg Gly Ala Arg His His Val Ala Phe Gly Phe Gly Val His Gln
340 345 350

Cys Leu Gly Gln Asn Leu Ala Arg Leu Glu Leu Gln Thr Val Phe Asp
355 360 365

Thr Leu Phe Arg Arg Val Pro Gly Ile Arg Ile Ala Val Pro Val Asp
370 375 380

Glu Leu Pro Phe Lys His Asp Ser Thr Ile Tyr Gly Leu His Ala Leu
385 390 395 400

Pro Val Thr Trp

<210> 64
<211> 1215
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic

<400> 64
atgaccgacg tcgaggaaac caccgcgacc ttgccactgg cccgcaaatg cccgttttca 60

ccaccgcccg aatacgagcg gctccgccgg gaaagtccgg tttcccgggt cggtctcccc 120

tccggtcaaa ccgcttgggc gctcacccgg ctcgaagaca tccgcgaaat gctgagcagt 180

ccgcatttca gctccgaccg gcagagtccg tcgttcccgc tgatggtggc gcggcagatc 240

cggcgcgagg acaagccgtt ccgcccgtcc ctcgtcgcga tggacccgcc ggaacacggc 300

aaggccaggc gtgacgccgt cggggaattc accgtcaagc gcatgaaagc gcttcagcca 360

cgtattcagc agatcgtcga cgagcatatc gacgccctgc tcgccggccc caaacccgcc 420

gatctcgtcc aggcgctttc cctgccggtt ccgtccttgg tgatctgcga actgctcggt 480

gtcccctatt cggaccacga gttcttccag tcctgcagtt cccggatgct cagccgggaa 540

gtcaccgccg aagaacggat gaccgcgttc gagtcgctcg agaactatct cgacgaactc 600

gtcacgaaga aggaggcgaa cgccaccgag gacgacctcc tcggccgcca gatcctgaag 660

cagcgcgaat ccggcgaagc cgaccacggc gaactggtcg gtctggcggc gctcctgctc 720

atcgcggggc acgagactac ggcgaacatg atctcgctcg gcacggtgac cctgctggag 780

aaccccgatc agctggcgaa gatcaaggca gatccgggca agaccctcgc cgcgatcgag 840

gaactcctgc ggatcttcac catcgcggag acggcgacct cacgcttcgc cacggcggac 900

gtcgagatcg gcggcacgct catccgcgcg ggtgaaggcg tcgtcggcct gagcaacgcg 960

ggcaaccacg atccggacgg cttcgagaac ccggacacct tcgacatcga acgcggcgcg 1020

cggcatcacg tcgccttcgg attcggtgtg caccaatgcc tcggccagaa cttggcgagg 1080

ttggaactcc agatcgtgtt cgatacgttg ttccggcgag tgccgggcat ccggatcgcc 1140

gtaccggtcg acgaactgcc gttcaagcac gattcgacga tctacggcct ccacgccctg 1200

ccggtcacct ggtag 1215

<210> 65
<211> 404
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic

<400> 65

Met Thr Asp Val Glu Glu Thr Thr Ala Thr Leu Pro Leu Ala Arg Lys
1 5 10 15

Cys Pro Phe Ser Pro Pro Pro Glu Tyr Glu Arg Leu Arg Arg Glu Ser
20 25 30

Pro Val Ser Arg Val Gly Leu Pro Ser Gly Gln Thr Ala Trp Ala Leu
35 40 45

Thr Arg Leu Glu Asp Ile Arg Glu Met Leu Ser Ser Pro His Phe Ser
50 55 60

Ser Asp Arg Gln Ser Pro Ser Phe Pro Leu Met Val Ala Arg Gln Ile
65 70 75 80

Arg Arg Glu Asp Lys Pro Phe Arg Pro Ser Leu Val Ala Met Asp Pro
85 90 95

Pro Glu His Gly Lys Ala Arg Arg Asp Ala Val Gly Glu Phe Thr Val
100 105 110

Lys Arg Met Lys Ala Leu Gln Pro Arg Ile Gln Gln Ile Val Asp Glu
115 120 125

```
His Ile Asp Ala Leu Leu Ala Gly Pro Lys Pro Ala Asp Leu Val Gln
    130                 135                 140

Ala Leu Ser Leu Pro Val Pro Ser Leu Val Ile Cys Glu Leu Leu Gly
145                 150                 155                 160

Val Pro Tyr Ser Asp His Glu Phe Phe Gln Ser Cys Ser Ser Arg Met
                165                 170                 175

Leu Ser Arg Glu Val Thr Ala Glu Glu Arg Met Thr Ala Phe Glu Ser
            180                 185                 190

Leu Glu Asn Tyr Leu Asp Glu Leu Val Thr Lys Lys Glu Ala Asn Ala
        195                 200                 205

Thr Glu Asp Asp Leu Leu Gly Arg Gln Ile Leu Lys Gln Arg Glu Ser
    210                 215                 220

Gly Glu Ala Asp His Gly Glu Leu Val Gly Leu Ala Ala Leu Leu Leu
225                 230                 235                 240

Ile Ala Gly His Glu Thr Thr Ala Asn Met Ile Ser Leu Gly Thr Val
                245                 250                 255

Thr Leu Leu Glu Asn Pro Asp Gln Leu Ala Lys Ile Lys Ala Asp Pro
            260                 265                 270

Gly Lys Thr Leu Ala Ala Ile Glu Glu Leu Leu Arg Ile Phe Thr Ile
        275                 280                 285

Ala Glu Thr Ala Thr Ser Arg Phe Ala Thr Ala Asp Val Glu Ile Gly
    290                 295                 300

Gly Thr Leu Ile Arg Ala Gly Glu Gly Val Val Gly Leu Ser Asn Ala
305                 310                 315                 320

Gly Asn His Asp Pro Asp Gly Phe Glu Asn Pro Asp Thr Phe Asp Ile
                325                 330                 335

Glu Arg Gly Ala Arg His His Val Ala Phe Gly Phe Gly Val His Gln
            340                 345                 350
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Cys Leu Gly Gln Asn Leu Ala Arg Leu Glu Leu Gln Ile Val Phe Asp
355 360 365

Thr Leu Phe Arg Arg Val Pro Gly Ile Arg Ile Ala Val Pro Val Asp
370 375 380

Glu Leu Pro Phe Lys His Asp Ser Thr Ile Tyr Gly Leu His Ala Leu
385 390 395 400

Pro Val Thr Trp

<210> 66
<211> 1215
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic

<400> 66
atgaccgacg tcgaggaaac caccgcgacc ttgccactgg ctcgcaaatg cccgttttca 60

ccaccgcccg aatacgagcg gctccgccgg gaaagtccgg tttcccgggt cggtctcccc 120

tccggtcaaa ccgcttgggc gctcacccgg ctcgaagaca tccgcgaaat gctgagcagt 180

ccgcatttca gctccgaccg gcagagtccg tcgttcccgc tgatggtggc gcggcagatc 240

cggcgcgagg acaagccgtt ccacccgtcc ctcgtcgcga tggacccgcc ggaacacggc 300

aaggccaggc gtgacgtcgt cggggaattc accgtcaagc gcatgaaagc gcttcagcca 360

cgtattcagc agatcgtcga cgagcatatc gacgccctgc tcgccggccc caaacccgcc 420

gatctcgtcc aggcgctttc cctgccggtt ccgtccttgg tgatctgcga actgctcggt 480

gtcccctatt cggaccacga gttcttccag tcctgcagtt cccggatgct cagccgggaa 540

gtcaccgccg aagaacggat gaccgcgttc gagtcgctcg agaactatct cgacgaactc 600

gtcacgaaga aggaggcgaa cgccaccgag gacgacctcc tcggccgcca gatcctgaag 660

cagcgcgaat ccggcgaagc cgaccacggc gaactggtcg gtctggcggc gctcctgctc 720

atcgcggggc acgagactac ggcgaacatg atctcgctcg gcacggtgac cctgctggag 780

aaccccgatc agctggcgaa gatcaaggcg gatccgggca agaccctcgc cgcgatcgag 840

gaactcctgc ggatcttcac catcgcggag acggcgacct cacgcttcgc cacggcggac 900

gtcgagatcg gcggcacgct catccgcgcg ggtgaaggcg tcgtcggcct gagcaacgcg 960

ggcaaccacg atccggacgg cttcgagaac ccggacacct tcgacatcga acgcggcgcg 1020

cggcatcacg tcgccttcgg attcggtgtg caccaatgcc tcggccagaa cttggcgagg 1080

ttggaactcc agatcgtgtt cgatacgttg ttccggcgag tgccgggcat ccggatcgcc 1140

gtaccggtcg acgaactgcc gttcaagcac gattcgacga tctacggcct ccacgccctg 1200

ccggtcacct ggtag 1215

<210> 67
<211> 404
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic

<400> 67

Met Thr Asp Val Glu Glu Thr Thr Ala Thr Leu Pro Leu Ala Arg Lys
1 5 10 15

Cys Pro Phe Ser Pro Pro Pro Glu Tyr Glu Arg Leu Arg Arg Glu Ser
20 25 30

Pro Val Ser Arg Val Gly Leu Pro Ser Gly Gln Thr Ala Trp Ala Leu
35 40 45

Thr Arg Leu Glu Asp Ile Arg Glu Met Leu Ser Ser Pro His Phe Ser
50 55 60

Ser Asp Arg Gln Ser Pro Ser Phe Pro Leu Met Val Ala Arg Gln Ile
65 70 75 80

Arg Arg Glu Asp Lys Pro Phe His Pro Ser Leu Val Ala Met Asp Pro
85 90 95

Pro Glu His Gly Lys Ala Arg Arg Asp Val Val Gly Glu Phe Thr Val
100 105 110

Lys Arg Met Lys Ala Leu Gln Pro Arg Il- :ln Gln Ile Val Asp Glu
115 120 125

His Ile Asp Ala Leu Leu Ala Gly Pro Lys Pro Ala Asp Leu Val Gln
130 135 140

```
Ala Leu Ser Leu Pro Val Pro Ser Leu Val Ile Cys Glu Leu Leu Gly
145                 150                 155                 160

Val Pro Tyr Ser Asp His Glu Phe Phe Gln Ser Cys Ser Ser Arg Met
                165                 170                 175

Leu Ser Arg Glu Val Thr Ala Glu Glu Arg Met Thr Ala Phe Glu Ser
            180                 185                 190

Leu Glu Asn Tyr Leu Asp Glu Leu Val Thr Lys Lys Glu Ala Asn Ala
        195                 200                 205

Thr Glu Asp Asp Leu Leu Gly Arg Gln Ile Leu Lys Gln Arg Glu Ser
    210                 215                 220

Gly Glu Ala Asp His Gly Glu Leu Val Gly Leu Ala Ala Leu Leu Leu
225                 230                 235                 240

Ile Ala Gly His Glu Thr Thr Ala Asn Met Ile Ser Leu Gly Thr Val
                245                 250                 255

Thr Leu Leu Glu Asn Pro Asp Gln Leu Ala Lys Ile Lys Ala Asp Pro
            260                 265                 270

Gly Lys Thr Leu Ala Ala Ile Glu Glu Leu Leu Arg Ile Phe Thr Ile
        275                 280                 285

Ala Glu Thr Ala Thr Ser Arg Phe Ala Thr Ala Asp Val Glu Ile Gly
    290                 295                 300

Gly Thr Leu Ile Arg Ala Gly Glu Gly Val Val Gly Leu Ser Asn Ala
305                 310                 315                 320

Gly Asn His Asp Pro Asp Gly Phe Glu Asn Pro Asp Thr Phe Asp Ile
                325                 330                 335

Glu Arg Gly Ala Arg His His Val Ala Phe Gly Phe Gly Val His Gln
            340                 345                 350

Cys Leu Gly Gln Asn Leu Ala Arg Leu Glu Leu Gln Ile Val Phe Asp
        355                 360                 365

Thr Leu Phe Arg Arg Val Pro Gly Ile Arg Ile Ala Val Pro Val Asp
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370 375 380

Glu Leu Pro Phe Lys His Asp Ser Thr Ile Tyr Gly Leu His Ala Leu
385 390 395 400

Pro Val Thr Trp

<210> 68
<211> 1215
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic

<400> 68
atgaccgacg tcgaggaaac caccgcgacc ttgccactgg cccgcaaatg cccgttttca 60

ccaccgcccg aatacgagcg gctccgccgg aaaagtccgg tttcccgggt cggtctcccc 120

tccggtcaaa ccgcttgggc gctcacccgg ctcgaagaca tccgcgaaat gctgagcagt 180

ccgcatttca gctccgaccg gcagagtccg tcgttcccgc tgatggtggc gcggcagatc 240

cggcgcgagg acaagccgtt ccgcccgtcc ctcatcgcga tggacccgcc ggaacacggc 300

aaggccaggc gtgacgtcgt cggggaattc accgtcaagc gcatgaaagc gcttcagcca 360

cgtattcagc agatcgtcga cgagcatatc gacgccctgc tcgccggccc caaacccgcc 420

gatctcgtcc aggcgctttc cctgccggtt ccgtccttgg tgatctgcga actgctcggt 480

gtcccctatt cggaccacga gttcttccag tcctgcagtt cccggatgct cagccgggaa 540

gtcaccgccg aagaacggat gaccgcgttc gagtcgctcg agaactatct cgacgaactc 600

gtcacgaaga aggaggcgaa cgccaccgag gacgacctcc tcggccgcca gatcctgaag 660

cagcgcgaat ccggcgaagc cgaccacggc gaactggtcg gtctggcgtt cctcctgctc 720

atcgcggggc acgagactac ggcgaacatg atctcgctcg gcacggtgac cctgctggag 780

aaccccgatc agctggcgaa gatcaaggcg gatccgggca agaccctcgc cgcgatcgag 840

gaactcctgc ggatcttcac catcgcggag acggcgacct cacgcttcgc cacggcggac 900

gtcgagatcg gcggcacgct catccgcgcg ggtgaaggcg tcgtcggcct gagcaacgcg 960

ggcaaccacg atccggacgg cttcgagaac ccggacacct tcgacatcga acgcggcgcg 1020

cggcatcacg tcgccttcgg attcggtgtg caccaatgcc tcggccagaa cttggcgagg 1080

ttggaactcc agatcgtgtt cgatacgttg ttccggcgag tgccgggcat ccggatcgcc 1140

gtaccggtcg acgaactgcc gttcaagcac gattcgacga tctacggcct ccacgccctg 1200

ccggtcacct ggtag 1215

<210> 69
<211> 404
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic

<400> 69

Met Thr Asp Val Glu Glu Thr Thr Ala Thr Leu Pro Leu Ala Arg Lys
1 5 10 15

Cys Pro Phe Ser Pro Pro Pro Glu Tyr Glu Arg Leu Arg Arg Lys Ser
20 25 30

Pro Val Ser Arg Val Gly Leu Pro Ser Gly Gln Thr Ala Trp Ala Leu
35 40 45

Thr Arg Leu Glu Asp Ile Arg Glu Met Leu Ser Ser Pro His Phe Ser
50 55 60

Ser Asp Arg Gln Ser Pro Ser Phe Pro Leu Met Val Ala Arg Gln Ile
65 70 75 80

Arg Arg Glu Asp Lys Pro Phe Arg Pro Ser Leu Ile Ala Met Asp Pro
85 90 95

Pro Glu His Gly Lys Ala Arg Arg Asp Val Val Gly Glu Phe Thr Val
100 105 110

Lys Arg Met Lys Ala Leu Gln Pro Arg Ile Gln Gln Ile Val Asp Glu
115 120 125

His Ile Asp Ala Leu Leu Ala Gly Pro Lys Pro Ala Asp Leu Val Gln
130 135 140

Ala Leu Ser Leu Pro Val Pro Ser Leu Val Ile Cys Glu Leu Leu Gly
145 150 155 160

Val Pro Tyr Ser Asp His Glu Phe Phe Gln Ser Cys Ser Ser Arg Met

165 170 175

Leu Ser Arg Glu Val Thr Ala Glu Glu Arg Met Thr Ala Phe Glu Ser
180 185 190

Leu Glu Asn Tyr Leu Asp Glu Leu Val Thr Lys Lys Glu Ala Asn Ala
195 200 205

Thr Glu Asp Asp Leu Leu Gly Arg Gln Ile Leu Lys Gln Arg Glu Ser
210 215 220

Gly Glu Ala Asp His Gly Glu Leu Val Gly Leu Ala Phe Leu Leu Leu
225 230 235 240

Ile Ala Gly His Glu Thr Thr Ala Asn Met Ile Ser Leu Gly Thr Val
245 250 255

Thr Leu Leu Glu Asn Pro Asp Gln Leu Ala Lys Ile Lys Ala Asp Pro
260 265 270

Gly Lys Thr Leu Ala Ala Ile Glu Glu Leu Leu Arg Ile Phe Thr Ile
275 280 285

Ala Glu Thr Ala Thr Ser Arg Phe Ala Thr Ala Asp Val Glu Ile Gly
290 295 300

Gly Thr Leu Ile Arg Ala Gly Glu Gly Val Val Gly Leu Ser Asn Ala
305 310 315 320

Gly Asn His Asp Pro Asp Gly Phe Glu Asn Pro Asp Thr Phe Asp Ile
325 330 335

Glu Arg Gly Ala Arg His His Val Ala Phe Gly Phe Gly Val His Gln
340 345 350

Cys Leu Gly Gln Asn Leu Ala Arg Leu Glu Leu Gln Ile Val Phe Asp
355 360 365

Thr Leu Phe Arg Arg Val Pro Gly Ile Arg Ile Ala Val Pro Val Asp
370 375 380

Glu Leu Pro Phe Lys His Asp Ser Thr Ile Tyr Gly Leu His Ala Leu
385 390 395 400

Pro Val Thr Trp

<210> 70
<211> 35
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (20)..(21)
<223> n=a, c, g or t

<400> 70
gttccgcccg tccctcgtcn nsatggaccc gccgg 35

<210> 71
<211> 35
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (15)..(16)
<223> n=a, c, g or t

<400> 71
cctgcagttc ccggnnsctc agccgggaag tcacc 35

<210> 72
<211> 1215
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic

<400> 72
atgaccgacg tcgaggaaac caccgcgacc ttgccactgg cccgcaaatg cccgttttca 60

ccaccgcccg aatacgagcg gctccgccgg gaaagtccgg tttcccgggt cggtctcccc 120

tccggtcaga ccgcttgggc gctcacccgg ctcgaagaca tccgcgaaat gctgagcagt 180

ccgcatttca gctccgacca gcagagtccg tcgttcccgc tgatggtggc gcggcagatc 240

cggcgcgagg acaagccgtt ccgcccgtcc ctcgtcgcga tggacccgcc ggaacacggc 300

aaggccaggc gtgacgtcgt cggggaattc accgtcaagc gcatgaaagc gcttcagcca 360

cgtattcagc agatcgtcga cgagcatacc gacgccctgc tcgccggccc caaacccgcc 420

gatctcgtcc aggcgctttc cctgccggtt ccgtccttgg tgatctgcga actgctcggt 480

gtcccctatt cggaccacga gttcttccag tcctgcagtt cccgggcgct cagccgggaa 540

gtcaccgccg aagaacggat gaccgcgttc gagtcgctcg agaactatct cgacgaactc 600

gtcacgaaga aggaggcgaa cgccaccgag gacgacctcc tcggccgcca gatcctgaag 660

cagcgcgaat ccggcgaagc cgaccacggc gaactggtcg gtctggcggc gctcctgctc 720

atcgcggggc acgagactac ggcgaacatg atctcgctcg gcacggtgac cctgctggag 780

aaccccgatc agctggcgaa gatcaaggcg gacccgggca agaccctcgc cgcgatcgag 840

gaactcctgc ggatcttcac catcgcggag acggcgacct cacgcttcgc cacggcggac 900

gtcgagatcg gcggcacgct catccgcgcg ggtgaaggcg tcgtcggcct gagcaacgcg 960

ggcaaccacg atccggacgg cttcgagaac ccggacacct tcgacatcga acgcggcgcg 1020

cggcatcacg tcgccttcgg attcggtgtg caccaatgcc tcggccagaa cttggcgagg 1080

ttggaactcc agatcgtgtt cgatacgttg ttccggcgag tgccgggcat ccggatcgcc 1140

gtaccggtcg acgaactgcc gttcaagcac gattcgacga tctacggcct ccacgccctg 1200

ccggtcacct ggtag 1215

<210> 73
<211> 404
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic

<400> 73

Met Thr Asp Val Glu Glu Thr Thr Ala Thr Leu Pro Leu Ala Arg Lys
1 5 10 15

Cys Pro Phe Ser Pro Pro Pro Glu Tyr Glu Arg Leu Arg Arg Glu Ser
20 25 30

Pro Val Ser Arg Val Gly Leu Pro Ser Gly Gln Thr Ala Trp Ala Leu
35 40 45

```
Thr Arg Leu Glu Asp Ile Arg Glu Met Leu Ser Ser Pro His Phe Ser
    50                  55                  60

Ser Asp Gln Gln Ser Pro Ser Phe Pro Leu Met Val Ala Arg Gln Ile
65                  70                  75                  80

Arg Arg Glu Asp Lys Pro Phe Arg Pro Ser Leu Val Ala Met Asp Pro
                85                  90                  95

Pro Glu His Gly Lys Ala Arg Arg Asp Val Val Gly Glu Phe Thr Val
            100                 105                 110

Lys Arg Met Lys Ala Leu Gln Pro Arg Ile Gln Gln Ile Val Asp Glu
        115                 120                 125

His Thr Asp Ala Leu Leu Ala Gly Pro Lys Pro Ala Asp Leu Val Gln
    130                 135                 140

Ala Leu Ser Leu Pro Val Pro Ser Leu Val Ile Cys Glu Leu Leu Gly
145                 150                 155                 160

Val Pro Tyr Ser Asp His Glu Phe Phe Gln Ser Cys Ser Ser Arg Ala
                165                 170                 175

Leu Ser Arg Glu Val Thr Ala Glu Glu Arg Met Thr Ala Phe Glu Ser
            180                 185                 190

Leu Glu Asn Tyr Leu Asp Glu Leu Val Thr Lys Lys Glu Ala Asn Ala
        195                 200                 205

Thr Glu Asp Asp Leu Leu Gly Arg Gln Ile Leu Lys Gln Arg Glu Ser
    210                 215                 220

Gly Glu Ala Asp His Gly Glu Leu Val Gly Leu Ala Ala Leu Leu Leu
225                 230                 235                 240

Ile Ala Gly His Glu Thr Thr Ala Asn Met Ile Ser Leu Gly Thr Val
                245                 250                 255

Thr Leu Leu Glu Asn Pro Asp Gln Leu Ala Lys Ile Lys Ala Asp Pro
            260                 265                 270
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Gly Lys Thr Leu Ala Ala Ile Glu Glu Leu Leu Arg Ile Phe Thr Ile
275 280 285

Ala Glu Thr Ala Thr Ser Arg Phe Ala Thr Ala Asp Val Glu Ile Gly
290 295 300

Gly Thr Leu Ile Arg Ala Gly Glu Gly Val Val Gly Leu Ser Asn Ala
305 310 315 320

Gly Asn His Asp Pro Asp Gly Phe Glu Asn Pro Asp Thr Phe Asp Ile
325 330 335

Glu Arg Gly Ala Arg His His Val Ala Phe Gly Phe Gly Val His Gln
340 345 350

Cys Leu Gly Gln Asn Leu Ala Arg Leu Glu Leu Gln Ile Val Phe Asp
355 360 365

Thr Leu Phe Arg Arg Val Pro Gly Ile Arg Ile Ala Val Pro Val Asp
370 375 380

Glu Leu Pro Phe Lys His Asp Ser Thr Ile Tyr Gly Leu His Ala Leu
385 390 395 400

Pro Val Thr Trp

<210> 74
<211> 1215
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic

<400> 74
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ccaccgcccg aatacgagcg gctccgccgg gaaagtccgg tttcccgggt cggtctcccc 120

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Thr Arg Leu Glu Asp Ile Arg Glu Met Leu Ser Ser Pro His Phe Ser
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Lys Arg Met Lys Ala Leu Gln Pro Arg Ile Gln Gln Ile Val Asp Glu
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His Ile Asp Ala Leu Leu Ala Gly Pro Lys Pro Thr Asp Leu Val Gln
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Val Pro Tyr Ser Asp His Glu Phe Phe Gln Ser Cys Ser Ser Arg Ser
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Thr Leu Phe Arg Arg Val Pro Gly Ile Arg Ile Ala Val Pro Val Asp
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Lys Ala Ala Leu Ser Asp Leu Arg Leu Ser Ser Asp Pro Lys Lys Lys
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Arg Leu Ser Ala Asp Glu Leu Thr Ser Ile Ala Leu Val Leu Leu Leu
225                 230                 235                 240

Ala Gly Phe Glu Ala Ser Val Ser Leu Ile Gly Ile Gly Thr Tyr Leu
                245                 250                 255

Leu Leu Thr His Pro Asp Gln Leu Ala Leu Val Arg Arg Asp Pro Ser
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Ala Leu Pro Asn Ala Val Glu Glu Ile Leu Arg T  Ile Ala Pro Pro
        275                 280                 285

Glu Thr Thr Thr Arg Phe Ala Ala Glu Glu Val Glu Ile Gly Gly Val
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Phe Gly Arg Phe Pro Ala Leu Ser Leu Gly Ile Asp Ala Asp Asp Val
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Val Trp Arg Arg Ser Leu Leu Leu Arg Gly Ile Asp His Leu Pro Val
385                 390                 395                 400

Arg Leu Asp Gly
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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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PCT/US2003/034082

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10/321,188 17 December 2002 (17.12.2002) US

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(74) Agents: **GOLIAN, Paul, D.** et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

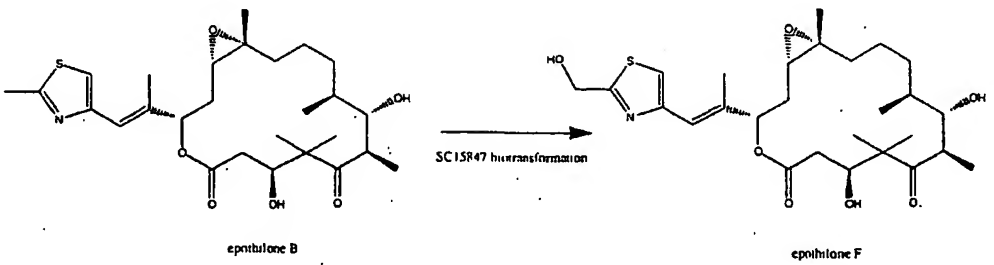
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
16 September 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPOSITIONS AND METHODS FOR HYDROXILATING EPOTHILONES



(57) Abstract: Isolated nucleic acid sequences and polypeptides encoded thereby for epothilone B hydroxylase and mutants and variants thereof and a ferredoxin located downstream from the epothilone B hydroxylase gene are provided. Also provided are vectors and cells containing these vectors. In addition, methods for producing recombinant microorganisms, methods for using these recombinant microorganism to produce hydroxyalkyl-bearing epothilones and an epothilone analog produced by a mutant of epothilone B hydroxylase are provided.

WO 2004/061116 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/34082

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 9/02, 1/20, 15/09; C07H 21/04
US CL : 435/189, 252.3, 252.33, 252.35, 320.1; 536/23.1, 23.2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/189, 252.3, 252.33, 252.35, 320.1; 536/23.1, 23.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/39276 (BRISTOL-MYER SQUIBB) 06 July 2000, see abstract.	8, 10
A		1-4, 6, 9, 11, 13, 20-26
A	CUPP-VICKERY et al. Structure of cytochrome P450eryF involved in erythromycin biosynthesis. Nature Structural Biology 1995, Vol. 2, No. 2, psges 144-153, see abstract.	6 and 11
A	CHANG et al. Construction of a 3D model of cytochrome P450 2B4. Protein Engineering 1997, Vol. 10, No. 2, pages 119-129, see abstract.	6 and 11
A	OMER et al. Gene for two herbicide-inducible cytochromes P-450 from Streptomyces griseolus. J. Bacteriol. June 1990, Vol. 172, No. 6, pages 3335-3345, see abstract.	1-4, 6, 8-11, 13, and 20-26
A	WATANABE et al. Gene 1995, Vol. 163, pages 81-85, see abstract.	1-4, 6, 8-11, 13, and 20-26.
A	MATSUOKA et al. Purification and characterization of cytochrome P-450sca from Streptomyces carbophilus. Eur. J. Biochem. 1989, Vol. 184, pages 707-713, see abstract.	8, 10, 11, and 13

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
30 April 2004 (30.04.2004)

Date of mailing of the international search report
21 JUL 2004

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer
Nashaat T. Nashed, Ph. D.
Telephone No. 703-308-0196

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/34082

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: Please See Continuation Sheet

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US03/3[redacted]82

Continuation of Box II Item 4:
1-4, 68-11, 13, and 20-26 as they pertain to SEQ ID NO: 1 & 2 as well as mutation at residue 43 of SEQ ID NO: 2.

Continuation of B. FIELDS SEARCHED Item 3:
Sequence search of SEQ ID NO; 1 & 2 in commercial databases, issued patents, and U. S. published application.
WEST: USPT, PGPB, USOC, EPAB, JPAB, and DWPI.
STN: MEDLINE, CAPLUS, SCISEARCH, LIFESCI, BIOSIS, and EMBASE.